FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE MEETING

MARCH 30, 2010

NTSB CONFERENCE CENTER

429 L'ENFANT PLAZA

WASHINGTON, D.C.

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JONATHAN DANIEL HECK, Ph.D.

JOHN H. LAUTERBACH, Ph.D.

Ex Officio Members:

URSULA BAUER, Ph.D.

ROBERT T. CROYLE, Ph.D.

H. WESTLEY CLARK, M.D.

FDA Participants:

LAWRENCE DEYTON, M.D.

CORINNE G. HUSTEN, M.D.

C O N T E N T S

C O N T E N T S (CON'T.)

P R O C E E D I N G S

DR. SAMET: Good morning. Let's get started.

I'm John Samet from the University of Southern California, and the Chair of the Tobacco Products Scientific Advisory Committee, which you are now going to hear referred to as TPSAC, with the addition of an "I" that's not there.

Thank you for joining us. I think -- by way of introduction I think that we all know that this is a historic moment for the FDA and for public health. There have been long foreseen need for regulation of tobacco products as a way to improve the public -- public's health.

The work of many has led us to this moment, the first meeting; Congress, of course, which passed the Act; the public health tobacco control communities that have provided scientific evidence and considered policy approaches to tobacco and public health.

There have been many giants who have contributed to this effort over the years. Some, of

course, no longer with us. Like, for example, Dr. Julius Richmond, former surgeon general; John Slade, Ron Davis, and others who we know well, and we know that there will be great interest on the part of many not only in the United States, but around the world in terms of the consequences of the new FDA Center and its actions.

I need to read some additional statements with regard to today's meetings for topics such as those being discussed at today's meeting. There are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meetings will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at

hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the Committee is reminded to, please, refrain from discussing the meeting topic during breaks or lunch. Thank you.

With that, let me ask for introductions of those sitting around the table starting, I think, with Dr. Croyle.

DR. CROYLE: Bob Croyle. I'm the Director of the Division of Cancer Control and Population Sciences at the National Cancer Institute here as the ex officio representative of the National Institutes of Health.

DR. BAUER: My name is Ursula Bauer. I'm the Director of the National Center for Chronic Disease Prevention and Health Promotion at the Centers for Disease Control and Prevention, here representing Dr. Frieden, Director of CDC.

DR. HECK: Hi, I'm Dan Heck, a principal scientist at the Lorillard Tobacco Company. I'm here representing the tobacco manufacturers.

DR. LAUTERBACH: I'm John Lauterbach. I'm owner of Lauterbach & Associates, LLC, a company that specializes in the chemistry and toxicology of tobacco products. And I'm here representing the small business tobacco manufacturers.

MR. HAMM: I'm Arnold Hamm. I'm representing the United States Tobacco Growers.

DR. BENOWITZ: Neal Benowitz, Professor of Medicine, University of California, San Francisco. I'm an internist, clinical pharmacologist, and medical toxicologist.

MS. DeLEEUW: I'm Karen DeLeeuw, and I am from the Colorado Department of Public Health and Environment. I'm representing state government.

MS. STARK: I'm Cristi Stark. I'm the Acting Designated Federal Official.

DR. CLANTON: I'm Mark Clanton, a pediatrician and currently Chief Medical Officer, the High Plains Division of the American Cancer

Society.

DR. HATSUKAMI: I'm Dorothy Hatsukami, University of Minnesota, Professor of Psychiatry.

DR. WAKEFIELD: Melanie Wakefield, Director of the Centre for Behavioural Research in Cancer at The Cancer Council Victoria, in Melbourne, Australia.

DR. HENNINGFIELD: I am Jack Henningfield, Vice President, Research and Health Policy, Pinney Associates, and professor in the Department of Psychiatry at the Johns Hopkins University School of Medicine. And my specialty is diction and pharmacology.

DR. NEZ HENDERSON: Good morning. My name is Patricia Nez Henderson. I am the Vice President of Black Hills Center for American Indian Health, a small nonprofit American Indian community based organization.

DR. CONNOLLY: Good morning. My name is Gregory Connolly. I am Professor at the Harvard School of Public Health, and the Acting Director of the Division of Public Health Practice.

DR. HUSTEN: Hello, I am Dr. Corinne Husten. I'm senior medical advisor in the Center for Tobacco Products at FDA.

DR. DEYTON: Good morning. I am Lawrence Deyton, Director of the Center for Tobacco Products at FDA.

DR. SAMET: Thank you. Let me turn next to Cristi Stark.

MS. STARK: Okay. I'm going to now read the Conflict of Interest Statement. The Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representatives, all members, temporary voting members, temporary nonvoting members, and the guest speakers are special government employees, SGEs, or regular federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and

conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetics Act, FD & C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance will Federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it's determined that the Agency's need for particular individual services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD & C Act Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of their interests of their own, as well as those imputed to them, including those of their spouse's or minor children; and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, gratis, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves, one, receiving presentations on the background and overview of the FDA Center for Tobacco Products, the Family Smoking Prevention and Tobacco Control Act -- known as the Tobacco Control Act -- and the Tobacco Products Scientific Advisory Committee.

Two, receiving presentations on and discussing the published literature on menthol as it relates to the demographics of users; preferential use by persons initiating tobacco use; the health effects of menthol and cigarettes; the effects of

menthol on addiction and cessation; marketing and consumer perceptions about menthol cigarettes; the sensory qualities of menthol cigarettes; and the effects of menthol on how cigarettes are smoked.

And three, receiving preliminary information about topics that we discussed at future meetings, including the establishment of a list of harmful and potentially harmful tobacco product constituents, including smoke constituents.

These discussions are preliminary to the preparation of the Tobacco Products Scientific Advisory Committee's required report to the Secretary of Health and Human Services regarding the impact of use of menthol in cigarettes on the public's health.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interest reported by the Committee members and temporary voting members no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all Committee members and temporary voting members to disclose any public statements that they have made concerning the issues before the Committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach, and Mr. Luby Hamm are participating in this meeting as non-voting industry representatives, acting on behalf of the interest of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers respectively. Their role at this meeting is to represent these industries in general and not any particular company.

Dr. Heck is employed by Lorillard Tobacco Company. Dr. Lauterbach is employed at Lauterbach & Associates, LLC; and Mr. Hamm is retired.

FDA encourages all of the participants to advise the Committee of any financial relationships that they may have with any firms at issue. Thank you.

Now, at this point I would like to remind

everyone present to, please, silence your cell phones if you have not already done so. I would also like to identify the FDA press contact.

Kathleen Quinn if you are here present, please stand. Thank you.

DR. SAMET: Okay. Thank you. I think we have been joined by Dr. Clark. If you could just do a quick introduction.

DR. CLARK: I am Westley Clark from the Substance Abuse and Mental Health Services Administration. I'm the Director in the Center for Substance Abuse Treatment.

DR. SAMET: Okay. Thank you. And today we're honored by having for our first meeting with us both Dr. Howard Koh, Assistant Secretary for Health; and Dr. Margaret Hamburg, the Commissioner of the FDA.

I'm pleased to introduce Dr. Koh, the 14th Assistant Secretary for Health, a position in which he oversees the department's Office of Public Health and Science, the commission core of the U.S. Public Health Service, and the Office of the Surgeon

General, along with serving as Senior Public Health Advisor to the Secretary.

Dr. Koh has a long record on tobacco control. As the Massachusetts Commissioner of Public Health, he was a national leader on smoking cessation and in developing cutting edge public health programs related to tobacco use.

Today at the request of Secretary Sebelius, Dr. Koh is leading a department-wide tobacco control working group committed to realizing a vision of a society free of tobacco-related death and disease.

I would add that many of us have had the pleasure of working with Dr. Koh on a variety of activities over the years. Welcome, and look forward to your remarks.

DR. KOH: Thank you so much. Welcome, everyone. It's an honor to be with you. I want to start with tremendous thanks to so many here. First, to my wonderful colleague and friend, Dr. Peggy Hamburg, Commissioner of the FDA.

Under Commissioner Hamburg's leadership we

are seeing tremendous strides in moving that agency toward a true public health mission. And her role and the role of Dr. Sharfstein, Dr. Deyton, and many others in the new Center for Tobacco Products is really very, very exciting in this new administration.

Dr. Deyton and his team at the new center have done extraordinary work, and we're very proud of their efforts in launching this Committee today, among other things; and he will continue to be a great leader in the area of tobacco control and regulation, and public health for the future.

I want to offer my special thanks to members of this new Tobacco Products Scientific Advisory Committee. You are experts. You are leaders in the world who have been recognized for your talents and your insights and your judgment. And we are absolutely thrilled to welcome you here today and to have you as partners working together to end suffering due to tobacco dependence in this country.

The timing of this meeting is absolutely

extraordinary. It's an extraordinary time to mobilize leadership in science and prevention for a healthier nation.

First, as we all know, the President has just signed a new health reform law that expands health coverage to millions of Americans; and that law has a special emphasis on prevention.

We also know that the President and Congress has invested $1 billion and more in prevention and wellness funding through the Recovery Act. Another sign of a commitment to prevention.

So we are here today to keep before us this dedication to prevention and wellness, and remind ourselves that our collective goal in public health through meetings such as this is to help each person reach what is known as their highest attainable standard of health. The highest attainable standard of health. And we need to do that through the efforts of this Committee and the efforts of everyone in this room.

We know the FDA is going to continue to be a leader in these efforts moving beyond its

traditional approaches of enforcing regulation and standards of safety and effectiveness through reaching higher public health standards in a broader public health approach. Again, we thank them for their leadership.

Also, at moments like this I think of the World Health Organization definition of health, which reads a complete -- a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. I love that definition. A state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity.

And the best way to reach these goals for all people in our country is through prevention and through public health, and that's what today's Committee and today's meeting is all about.

In short, our good health is a gift and we need to protect that gift through the work of this group that's gathered here.

As you heard from our Chairman, I have a particular commitment to this area as a physician

who has cared for patients for over 30 years, as a former state health commissioner, as a researcher, as a former professor, and now as the Assistant Secretary for Health. And in fact, my very first day on the job as Assistant Secretary was on June 22nd, 2009 after being nominated by the President and being confirmed by the United States Senate.

And on that day, Monday, June 22nd, 2009, I found myself in the Rose Garden observing as the President signed the Family Smoking Prevention and Tobacco Control Act into law. So for me that was a sign that public health and prevention had entered a new era; and to be part of that is a tremendous privilege for me personally.

That's why it was an honor to join Commissioner Hamburg and FDA leaders last September when the FDA announced a ban on cigarettes with flavors characterizing fruit, candy or clove, which science has shown are often a gateway to smoking for children and adolescents. That's why it was a privilege for me to join Commissioner Hamburg and

FDA leaders last week when the FDA issued a final rule that contains a broad set of federal requirements designed to significantly curb access to, and the appeal of cigarettes and smokeless tobacco products to children and adolescents in our country.

We all know that this new rule becomes effective on June 22, 2010, the first anniversary of the Family Smoking Prevention and Tobacco Control Act. So, in short, we are entering a new era of tobacco prevention and control in this country.

As you heard from Dr. Samet, in November of 2009 Secretary Sebelius charged the department with developing a department-wide strategic action plan for tobacco control, and charged our workgroup to develop a plan to realize the vision of a society free of tobacco-related death and disease.

I want to thank my colleagues from Health and Human Services, particularly Rosie Henson, Cliff Douglas, Simon McNab (phonetic), and many others who have worked this plan, which is nearing completion. We want to achieve a vision where we have a

healthier people. And as the Assistant Secretary for Health I also oversee the Healthy People Process; and we have four Healthy People 2020 tobacco control goals: To reduce tobacco use by adolescents and adults; to reduce the initiation of tobacco use among children, adolescents, and young adults; third, to increase recent smoking cessation success by adult smokers; and fourth, to reduce the proportion of nonsmokers exposed to secondhand smoke.

We want to do this all at the department while also actively supporting the FDA's newly acquired role as a public health agency that regulates the sale, distribution, advertising and promotion of tobacco products. So in short, this is quite a day for public health. We want to thank you for your commitment to prevention and to public health, and to making the next generation healthier. Thank you very, very much.

DR. SAMET: Thank you, Dr. Koh.

I'm pleased to introduce the Commissioner of the Food and Drug Administration, Dr. Peggy

Hamburg. She is exceptionally well qualified to lead the nation's premiere regulatory agency given her training and experience as a physician, scientist, and public health executive.

Dr. Hamburg has served as Commissioner of New York City Department of Health and Mental Hygiene, and is Assistant Secretary for Policy and Evaluation in the U.S. Department of Health and Human Services. Her commitment to science was clear on the day that President Obama signed the Family's Smoking Prevention and Control Act, and it continues in full force today as she takes time out from her schedule to join us as we set out on our mission.

I know I speak for all our Committee members who are grateful for Dr. Hamburg's vision and leadership in establishing the Center for Tobacco Products at the FDA, and for helping to create the TPSAC and being involved in selecting us. Dr. Hamburg.

DR. HAMBURG: Thank you very, very much. Thank you all for being here today, and for your willingness to serve on this very important

Scientific Advisory Committee.

Thank you, Dr. Koh, also for your leadership within the department, and your willingness over many, many years to be out front on important issues that really matter to health and well-being. This is an historic day. We also must recognize that we have a lot of work before us.

So I will try to be relatively brief so that you all can, in fact, roll up your sleeves and get down to the job before you. I hope that you are ready and eager to dive into this enormous task, this great public health challenge that we have all been charged with tackling together. There is an enormous amount to be done, and clearly, the issues won't all be easy. We, I think, can all agree on that.

But as Dr. Samet mentioned, we come here today standing on the shoulders of giants who have done important work before us. People that committed their lives to working on the tobacco issue, and people that committed their lives to working on broader public health issues. But it is

inspiring and I think that we all should, you know, have a real sense that today and going forward we are engaging in work that will have real and enduring value to our generation, and importantly to the generations that come.

I was talking this morning with Dr. Deyton about the story of Dr. John Snow. And those of you in public health know, of course, this story; but let me mention it for those of you who don't. Because I think that it is a wonderful story that we should bear in mind as we think about the decisions that will affect the lives of so many Americans.

Dr. Snow was a physician practicing in London during the middle part of 19th century. A time when the city was facing a series of severe cholera epidemics. Epidemics that were very disruptive not just to health, but to the social fabric of the city and the emotional well-being of the people in that community; and, of course, in others also hit by the problem of cholera.

Most doctors back then believed that cholera was caused by what people called bad air

miasma; but Dr. Snow had a theory of his own. He suspected that the disease had one common origin. So he painstakingly plotted, mapped out each and every case of cholera in the city. And sure enough he found through this work that every case of cholera could be traced back to a single water pump.

So Dr. Snow, I think, was very important in that he had a simple solution to a complicated and dangerous epidemic. And his solution was science based. He looked at the information, and he asked critical questions, and he didn't allow himself to be overwhelmed by mythologies about the cause of disease or the emotionally laden nature of the disease in a community, in a population.

When he acted on his information and they removed the handle of the pump, the rates of cholera dramatically went down. It was a brilliant public health move, and it marked a new era in public health. I think that it is a clear and compelling example of bringing science to bear on important health problems. An example of how informed action can make a difference to the health and well-being

of populations, and can bring true informed scientific understanding to a set of issues that can be very complex and confusing.

I mention this, because we too are on the cusp of a new era in public health. You, the members of this Committee, have a chance to make history. You have a chance to provide scientific input and expertise as we address one of the most pressing public health problems of our day. You have a chance to weigh in on implementing the Tobacco Control Act. You have a chance to help us at the FDA take the handle off the proverbial pump. So that together we can fight lung cancer, coronary heart disease, strokes, emphysema, and the staggering half million or so deaths caused by tobacco every year.

This Committee is not charged with interpreting the Tobacco Control Act. Believe me, we have a whole retinue of lawyers and policy makers that are helping us with those important tasks of helping to draft the Regulations, et cetera. But your role is really unique, and it is really, really

important. Probably more important than what all our lawyers and regulatory experts are doing, because you provide the scientific foundation that will guide FDA in the crafting these Regulations, which includes examining the effects of altering nicotine yields in tobacco products; and determining whether there are threshold levels below which nicotine yields don't produce dependence.

The overarching mission of this Committee is to provide the advice, information, and recommendations necessary to effectively regulate tobacco products. Today you are jumping into the science with a meeting that will be focused on menthol in cigarettes, an area that has been much discussed. There has been important scientific work; but where I think we need the input of this Committee to help guide us as we move forward in our Regulations and our actions at the FDA.

But, of course, your work won't stop with grappling with that important issue. You will be asked over months and years to come to help us explore other important safety dependence or health

issues as they emerge. And I'm sure that you all understand, but I want to underscore it once again, that the FDA regulation of tobacco products is a science based, science driven process. It must be. And you are the men and women mandated to provide us with the best available science.

So on behalf of all of us at FDA, I want to extend my sincere appreciation to all of you for your commitment and for your service, and to an issue that is so important to our nation and to the world. And as FDA embarks on its regulation of tobacco products, we are working closely with partners around the world. We have colleagues with us today.

But I think that -- that what you are doing, while a national effort, does represent an international activity; and I think it's humbling but important to recognize that as well. That in many aspects you are setting standards and delineating pathways that will be followed by many others around the world.

So it's a big task and it's one that I

know all of you are committed to or you wouldn't be here; but we thank you. We want to support you in your efforts in anyway that we can. I especially want to thank Dr. Samet for taking on the role of Chair, which is such a key position. And I know he brings the skills and dedication to lead you all in extraordinary ways.

I also want to thank Dr. Deyton and his amazing team for the work that they have done to stand up the new Center for Tobacco Products, to begin to implement the tobacco legislation, as Dr. Koh indicated; and for putting together the Scientific Advisory Committee, and this first meeting. I know that it is going to be a fascinating challenging undertaking. I am very pleased to be here as you kick off a very full day, and I wish you all the best of luck. Thank you.

DR. SAMET: Thank you, Dr. Hamburg. And I'm sure a month from now or a year from now, and several years from now we will know just how big an undertaking we are all going after.

With that, I will turn to Dr. Deyton, and

let me do an introduction. First, he was selected after a national search by Dr. Hamburg as the first Director of the Center for Tobacco Products in September of 2009. He comes to FDA after a distinguished career in public health where he has been a researcher at the National Institute of Allergy and Infectious diseases, and served in the Office of the Assistant Secretary for health -- of the Department of Health and Human Services, and its original office of smoking and health.

Dr. Deyton also served as the Chief Public Health and Environmental Hazards Officer for the Department of Veterans Affairs where one of its priorities was revitalization of the VA's smoking and tobacco use cessation programs. Under his leadership current smoking among veterans enrolled in the cessation program fell from 33 percent in 1999 to 22 percent in 2007.

I also think it's significant and representative of his commitment to health and well-being of others in that he sees and treats patients at a VA clinic every week -- apparently not

today. It's with great pleasure that I introduce Dr. Deyton.

DR. DEYTON: Thank you very much, Dr. Samet, and thank you all for being here today. There really are very many people to thank for helping to get this meeting together; and there are many people who have been involved in the creation of this organization, the Tobacco Products Scientific Advisory Committee, or TPSAC, as we call it.

Two people who deserve special recognition for their incredible ongoing support are Commissioner Peggy Hamburg, and Assistant Secretary for Health, Dr. Howard Koh, who you have just heard from. They recognize, as all of us around the table and at the Center for Tobacco Products, that the Tobacco Control Act not only represents a new commitment to protecting Americans from the danger of tobacco. It also embodies a new strategy to promote public health. That's why as soon as the President signed The Family Smoking Prevention and Tobacco Control Act, Dr. Hamburg and Deputy

Commissioner, Josh Sharfstein moved quickly to create the Center for Tobacco Products, and to begin the work of fulfilling FDA's new responsibility in Tobacco Product Regulation.

At the same time Dr. Koh began to organize HHS-wide tobacco control activities to ensure FDA had optimal support from and integration with our sister public health agencies. And I'm proud to say that in mid-August, not long after the Center was created, I had the honor of becoming its first employee.

Since then, our work has been to build an organization with the staff necessary to take the first steps of FDA's tobacco product regulation by implementing the law based on the best science.

The Tobacco Control Act is simply an amazing piece of legislation. Drs. Koh and Hamburg have already described the critical importance of the public health mission embodied in it. At it's core is the understanding that by adding important regulatory authority to the scientific base, and the public health tools already in place supporting

tobacco control, we can further reduce the tremendous toll of disease, disability, and death caused by tobacco products.

That's why the FDA's new authorities include restricting the marketing of tobacco products to minors, banning the manufacture, sell, distribution of cigarettes with certain candy and characterizing flavors, requiring new graphic warning labels for cigarettes and smokeless tobacco, prohibiting the marketing measures that mislead consumers. And for the first time ever, establishing tobacco product standards.

Also, by requiring good manufacturing practices for tobacco manufacturing facilities, requiring FDA approval of any products claiming to have a modified risk, requiring industry reporting of tobacco product ingredients and constituent data, and educating Americans about tobacco product constituents that are harmful or potentially harmful to their health, and the health of others. And, of course, using our enforcement authorities, for FDA to act quickly and effectively to remove products

that are in violation, and to enforce all the provisions of the Family Smoking and Prevention and Tobacco Control Act.

The Tobacco Control Act gives us an ambitious agenda, but the Center for Tobacco Products has hit the ground running to implement it. You will hear more details about our enabling legislation from the Center's senior counsel, Catherine Lorraine in just a moment.

I want to highlight the incredible work our staff has done since Dr. Hamburg launched the Center in August. We created the Tobacco Product User Fee Program and begin collecting user fees that supports the work of the Center. As I mentioned, and as Dr. Hamburg and Koh mentioned, we implemented the ban on the manufacture, sell, and distribution of cigarettes with certain candy and fruit characterizing flavors. We issued the final guidance on industry registration with the FDA, and submission of listings of their products and ingredients and constituents of those products. We established a new office to assist small tobacco

manufacturers in their compliance with the Tobacco Control Act.

And as you know, and as was just discussed this month, just last week, we reissued the 1996 rule, which mandates a range of actions not only to reduce the access of cigarettes and smokeless tobacco to kids, but also their attractiveness.

And today has begun the process of contracting with each state and territory to assist FDA in enforcing the provisions of the 1996 rule. But these aren't the only priorities we have had at the Center for Tobacco Products. Of course one of the most important activities has been organizing and launching this meeting and this group.

And let me say this as plainly as I can; we at the FDA absolutely require your collective voice, the Tobacco Products Scientific Advisory Committee; your scientific expertise, and your advice to guide us.

You have some specific assignments outlined in the law, which the Center's senior medical advisor, Dr. Corrine Husten, will review in

just a short while. These include your assessments at this meeting, advising us on the issue of menthol, which Dr. Hamburg talked about; and you will have other assignments in the near future.

We will also be turning to you in the future for your best scientific advice on any number of issues important to the FDA responsibilities for tobacco product regulation.

So, in short, we need you to be exactly what you are, the best and the most experienced minds representing a wide array of expertise and disciplines. And I want to add that the expertise and advice we need isn't limited to the voting members of the Committee.

As you know, the Tobacco Control Act requires that this Committee have three non-voting members representing the tobacco industry. And there is a reason for that. It's because a precondition for designing effective regulatory measures is understanding the industry to be regulated, and the tobacco industry is no exception.

So successful implementation of the

Tobacco Control Act requires engaging the various components of the tobacco industry directly, fairly, and with transparency. And I should add that at the Center for Tobacco Products we already have done so in certain ways. I know the input the Center received from a wide variety of companies, large and small, was helpful in establishing a system for industry registration with FDA, and submission of listings of tobacco products. And it's my hope that that experience can help set the tone for this committee's work in the months and years to come.

The bottom line is that when Congress passed, and President Obama signed the Tobacco Control Act into law, it was with the understanding that the traditional approach to product regulation wasn't relevant in the case of tobacco. In this instance, FDA's traditional standards of safety and effectiveness don't work; but a public health population health standard does, and that is what the Tobacco Control Act requires us to use.

So under the guidance of the Tobacco and Control Act, and with your scientific advice we are

creating a new standard, and its application to our authorities to regulate tobacco products. And with the goal of that standard is to reduce the tremendous toll of disease, disability, and death caused by tobacco products.

Can we succeed?

There is not a doubt in my mind that we can; but only if we're guided by the best science. And that's why the work of this Committee is so fundamental to FDA's mission. The advice you give us based on the science and the science alone will help us at FDA shape regulations and programs that will literally save people's lives and make America a healthier nation; but that's not all. We're also striving to create a transparent process that Americans know they can trust. That's always critical at any regulatory system, but history tells us it is absolutely fundamental to regulating tobacco products.

When Americans look at the advice you present to FDA, they're going to know that everyone had a seat at the table, and different stakeholders

were heard. But they are also going to know something else, that in the end the advice you gave us to improve and protect the health of all Americans was built on a solid foundation of science.

So I commit the full support and resources of the Center for Tobacco Products to assist you, the Tobacco Products Scientific Advisory Committee, in the work that you will be doing; and I thank you.

I thank you for agreeing to join this Committee. I thank you for the work you are about to commence; and thank you for fulfilling what is now your role in implementing the Family Smoking Prevention and Tobacco Control Act. Thank you very much and good luck.

DR. SAMET: Thank you, Dr. Deyton, and look forward to getting on with the work.

Our next speaker is Catherine Lorraine from the Center, who will provide an overview of the Family Smoking Prevention and Tobacco Control Act.

MS. LORRAINE: Good morning. It's a real pleasure to be here with Assistant Secretary Koh,

our Commissioner, Dr. Hamburg, with this distinguished Committee, and my colleagues from the FDA on this very historic day.

I'm going to help set the stage for today's discussions and presentations by giving a very short overview of the Family Smoking Prevention Tobacco Control Act, say a few words about our goals at the FDA, and -- overeager clicker here -- and talk a little bit about our accomplishments, and highlight some upcoming regulatory milestones in our future.

Our goals are very clear at the FDA. We want to prevent youth from using -- ever beginning to use tobacco products. We want to help adults who use those products quit as quickly as possible to improve their health; and we want to help the public understand the contents of tobacco products, and the serious and awful, in many cases, consequences of using those products. And importantly for this Committee we want to help develop the science base and begin meaningful product regulations.

The scope of our authority under the

Tobacco Control Act is quite clear. FDA is given authority to regulate tobacco products, which are defined as products made or derived from tobacco and intended for human consumption.

It's important to note that tobacco products do not include drugs or devices which are regulated under separate provisions of the Federal Food, Drug and Cosmetic Act. The Act now recognizes the FDA as the primary federal authority regulating tobacco products with respect to manufacturing, marketing, and distribution.

The statute is modeled in great part on the medical advice amendments to the Food, Drug and Cosmetic Act. It contains a variety of provisions that relate to pre-market review, post-market surveillance, performance, standing, testing, and reporting of ingredients; adverse event reporting; and requires new warning labels, among other things.

I'm going to start now and just give a very brief highlight of a number of provisions in the Act. Section 904 is a provision that requires manufacturers and others to provide a variety of

information, including ingredients and constituents of tobacco products to the Agency. It also requires manufacturers to report a variety of different types of health information in their possession about tobacco products. And this provision requires the Agency to establish a list of harmful or potentially harmful constituents of tobacco products.

Section 905 is a core provision in the Act for us. It requires manufacturers to list and register -- list their products and register their establishments with us. This gives us the information that we need to send our field force out to conduct inspections, which must be done on a biannual basis.

Section 907 is the authority to establish tobacco product standards. This gives the Agency the ability to set standards regarding the content and design of tobacco products. It is the provision of the law that directs the referral of the issue of menthol and tobacco products to this Advisory Committee.

The Secretary is not allowed under this

law to either ban a class of tobacco products or to reduce the level of nicotine in tobacco products to zero. That authority is reserved to the Congress.

Section 910 is the provision that allows the regulation of new tobacco products, and all new products are required to submit an application to the Agency for review and order unless these products have been determined to be substantially equivalent to already commercially marketed products. The application must require -- will require a variety of different information about the composition of the product, the labeling of the product, and health effects of the product, among other things.

911 is the authority to regulate modified risk tobacco products. And these are described in the statute as those that are sold and distributed to reduce the harm or the risk of tobacco-related disease. And the information that must be submitted to the Agency must clearly demonstrate that. There will be -- there are special rules that apply to products whose sole claim is to reduce or eliminate

harmful substances. Applications received under this provision are automatically referred to this Committee for their review.

Section 919 is the authority to collect user fees from the industry, and all activities to implement this statute must be funded by user fees. We began collection of those fees in October; and that activity will be ongoing to support all the activities of the Center.

Section 201 gives the Agency the authority to establish new warnings and -- including graphic images for cigarette products. These requirements go into effect in June of 2011. The new addition to the law here will be the requirement that there be color graphics that accompany these warnings depicting the negative consequences of tobacco use.

Smokeless tobacco products are also subject to new warning requirements, with the addition of rotational warning plans that have to be submitted to the Agency for our approval; and smokeless tobacco products will now no longer be able to be advertised on any medium subject to the

jurisdiction of the Federal Communications Commission.

Some of the accomplishments of the Center -- I will just briefly go over them. Dr. Deyton eluded to a number of them. But the law was signed into effect by the President on June 22nd, 2009, a very warm day in June. In July and through the summer we held a number of listening sessions with various stakeholders. We established the Center officially, found a home for ourselves.

In September we were very fortunate to have Dr. Deyton begin as the first director of our Center, and we implemented the flavor ban on certain candy, herb, and fruit flavors characterizing cigarette products.

Throughout the fall we were in developing and issuing guidance for industry about ways that they could implement -- that they could comply with the requirements in the law, especially those related to Section 904 and 905. And in March, as Dr. Deyton also mentioned, we issued the 1996 Rule on youth access and advertising. And we are -- we

have announced a competition for states to apply for contracts to help us enforce the provisions of those regulations.

This coming June, June 22nd, specifically, will be a very important month for us. It will be the first anniversary of the signing of the law into effect by the President. It also is the date on which descriptors, such as light, low, and mild become illegal on tobacco products. It is the date on which the new warning statements for smokeless tobacco goes into effect; and it is the effective date of the 1996 Rule.

I want to just end by giving you our web site where I urge you to go. We have a wealth of information there on provisions of the law and the activities of the center, and you can sign up for automatic notification of certain actions. So please do visit us at our web site. Thank you very much.

DR. SAMET: Thank you. We will move on now to Dr. Corinne Husten who is going to provide an overview of the TPSAC itself. And we're actually

running so far ahead that maybe we could move into your second presentation if that works before -- before break.

DR. HUSTEN: I think that's great.

What I would like to do, first, is to just talk about what's in the statute specifically regarding the Tobacco Products Scientific Advisory Committee. As you know, this statute requires the Secretary to establish a 12-member Advisory Committee, which is -- as was mentioned, is affectionately known as TPSAC, because that's too many words to keep saying everytime.

The members are to be appointed with very specific criteria. The members need to be individuals who are technically qualified by training and experience in medicine, medical ethics, science, or technology involving the manufacture, evaluation, or use of tobacco products; and we're also required to have a committee of diversified professional backgrounds. And I would like to note that this criteria applies to all members, both voting and non-voting members.

The Committee is to have some very specific types of voting members, including seven individuals who are physicians, dentists, science, or health care professionals in a variety of disciplines.

One individual who is an officer or employee of a state or local government, or potentially also the federal government; and one individual who is a representative of the general public.

There are also, as was mentioned, three non-voting members, including an individual representing the tobacco manufacturing industry; one representing the small business tobacco manufacturing industry; and one individual representing tobacco growers.

No member of the Committee who is a voting member can, during the time while on the Committee or in the 18 months prior to serving on the Committee, have received any salary, grants, or other payments, or support from the tobacco industry. There are other federal conflict of

interest statutes, regulations, and guidance that apply as you heard with our conflict of interest statement that was read at the beginning of the meeting.

There are some specific duties of the Advisory Committee that are laid out in the law. The TPSAC shall provide advice, information, and recommendations to the Secretary on the effects of alteration of nicotine yields from tobacco products; whether there is a threshold below which nicotine yields do not produce dependence; and reviewing other safety, dependence, or health issues related to tobacco products as requested by the Secretary.

Then there are other provisions in other parts of the statute that include the impact of the use of menthol in cigarettes on the public health, which is the topic of this first meeting. The nature and impact of use of dissolvable tobacco products on public health; and as you heard, any application submitted for a modified risk tobacco product.

The menthol report has some very specific

requirements. Immediately upon establishment of the TPSAC, the Secretary shall refer to the Committee for report and recommendation the issue of the impact of the use of menthol in cigarettes on public health, including its use among children, African Americans, Hispanics, and other racial and ethnic minorities.

There are some other specific things that the Committee needs to take into account that I will reserve for the next talk that gives more specifics about the menthol report.

There is also a second report that the Committee is required to produce, and that's a report and recommendations on the use of and the impact of dissolvable tobacco products on the public health, including such use among children. That report is due no later than two years after the establishment of the Committee; and so that report is due March 23 in 2012.

Any questions specifically about the statutory requirements of the Committee?

Okay. Then maybe I can move into some of

the specifics of the menthol report.

As I eluded to, there is a specific requirement in the statute for the Committee to evaluate the impact of use of menthol in cigarettes on public health. As I mentioned, it was a topic that had to be immediately referred to the Committee, so that's why it's the topic of our first meeting.

There are some very specific things that the Committee is asked to address in its review of this topic. One is, the risks and benefits to the population as a whole, including both nonusers and users of tobacco products. The increased or decreased likelihood that existing users of tobacco products will stop using. The increased or decreased likelihood that those who do not use tobacco products will start using such products. The technical achievability of any recommendations; and the potential for any recommendations to have effects on adolescent and adult users, and non-tobacco users; and the creation of significant demand for contraband.

So the statute has some very specific considerations that we are asking the Committee to take into account when they develop their reports and recommendations.

The report on menthol is due not later than one year after the establishment of the TPSAC; and so it's due March 23rd, 2011. And what we wanted to make sure that this first meeting -- since the Committee was just established there wasn't a lot of time, obviously; we wanted to prepare some materials so the Committee had some information to start addressing this topic.

And so what we did is we looked at the published research that we could find on some specific topics related to menthol that could be presented to the Committee and would get a start on what's out there in terms of the published literature so the Committee could start thinking about what other information they need to complete this report.

So you are going to hear a series of presentations on a series of topics related to

menthol in cigarettes, including the use of menthol by various demographic groups; menthol cigarettes and smoking initiation; the marketing of menthol and consumer perceptions; menthol sensory qualities and topography; menthol's effect on nicotine dependence; menthol smoking cessation behavior; and the health effects on mentholated cigarettes.

But the primary purpose of this first meeting is to really -- for the Committee to start thinking about and telling us what you will need and what approach you want to take to completing the report within the statutorily required deadline of one year.

We had also -- since we want to have a second meeting relatively soon -- hopefully in the summer -- we wanted to also put on the table at least some considerations that we were thinking about for topics for the second meeting, but, obviously, this is a topic for you to discuss, and what you want to happen at the second meeting. But our initial considerations were that we felt we would provide to you an analysis of tobacco industry

documents in the Legacy Tobacco Documents Library on menthol cigarettes and nicotine dependence; menthol cigarettes and initiation; and marketing and consumer perceptions.

And that the second meeting would also have a substantial amount of time devoted to industry presentations with an emphasis especially on unpublished data and a focus on marketing of menthol cigarettes, initiation, consumer perception, nicotine dependence, and cessation.

Again, this is just put out there for your consideration. We want to hear from you about what you really want to have as topics for the second meeting, and other information that you need; but we needed to do some preparation if we were going to have a meeting in the summer, and so we started at least moving forward with some analysis of the tobacco industry documents in the Legacy database.

So the questions that ultimately you will need to address in your final report are, what is the impact of menthol cigarettes on public health, including such use among children, African

Americans, Hispanics, and other racial and ethnic minorities? And what recommendations, if any, does TPSAC have for FDA regarding menthol cigarettes?

Now, obviously, those aren't questions that you can answer at this first meeting, because you don't have full information; but I wanted to make sure that you kept those two questions in mind as you are thinking about what you will need in the subsequent meetings; and to -- you know, for us to prepare for you.

The specific questions for this meeting that we would like you to address are, are there any specific questions around menthol that the industry should address at the next meeting, since we do want industry presentations at the second meeting since there wasn't really the ability to give industry time for this meeting to make presentations?

What other information does the Committee need in order to meet its statutory requirements?

Are there agenda items that should be included in future meetings pertaining to menthol?

And what support does the Committee need

to complete its report and recommendations by the statutory deadline?

So we will bring these questions back to you when you get to the discussion period; and again, the primary focus of this meeting is really to tell us what you need in order to get this report done.

So any questions about your initial charge with -- which is to start working on developing this report which is due in a year.

DR. SAMET: Okay. So this is the opportunity for the Committee to ask clarifying questions. Greg.

DR. CONNOLLY: Thank you very much. It was an excellent presentation. On your slide, initial approach to the second meeting, you referenced -- go back to that slide -- you reference analysis of tobacco industry documents in the Legacy Document Library. Just for a point of clarification, has FDA been delivered other documents that were not placed in the Legacy Document Library when the Attorney General settled

the court case?

DR. HUSTEN: We have no documents. What we have -- we prepared for this meeting a review of published literature -- at least what we could find in the published literature on the various topics; and then we have asked -- we have a contract to start looking at these specific issues in the Legacy Document Database.

DR. CONNOLLY: Thank you.

DR. HUSTEN: Any other clarifying questions?

DR. WAKEFIELD: Corinne, just for background, the -- the articles and so forth that you have provided us with, could you give a bit of an overview about how you came across those articles? You got to use search terms and that sort of thing.

DR. HUSTEN: Actually, the very first presentation after the presentation on the demographics will actually walk you through exactly how we found the documents that we have. If you wouldn't mind just defraying that; because it

probably flows, you know, better as you start to see. Then we will also talk about each topic, how many articles we found. Obviously, you know, if we have missed any articles we will want you to let us know that.

DR. WAKEFIELD: Yes. And I guess a follow-up question is that's fine for what we have now. I guess all of us probably know there is work in progress that's going on right now, articles that may get accepted for publication. What's the process of bringing new information before the Committee and ensuring that we are up-to-date so that our report includes the very latest research?

DR. HUSTEN: Well, we certainly can continue to monitor the published articles. We would also ask you as you are aware of things to let us know, so that we can make sure we aren't missing anything that you need.

DR. SAMET: I have two questions, and they relate to, I think, interpretation of our charge. So menthol cigarettes versus menthol in cigarettes as one. And I know -- noted in my background

reading that menthol is a -- commonly used in cigarettes -- some cigarettes that are mentholated have a higher concentration. So what is our charge? As read specifically it's menthol cigarettes.

Then, the other question just is one simply of a more complicated matter of interpretation; what is the impact of menthol cigarettes on public health implies a comparison to something. Presumably a world in which menthol cigarettes don't exist.

I mean, the big word for this is counterfactual. And what -- how is that thought of -- how have you thought of that. Perhaps, we should have some discussion. Both matters -- menthol in cigarettes versus menthol cigarettes, and then the question of comparison for impact.

DR. HUSTEN: Well -- and to some extent those are decisions that you are going to have to make, because we all have just what's in the statute to guide us. Certainly, as we were looking at the literature we were comparing the mentholated cigarettes to the nonmenthol cigarettes, as they're

generally considered. So cigarettes that have menthol more as an unique flavor compared to ones that are considered the nonmenthol cigarettes, even if they all contain some menthol.

Certainly, around health effects, you know, it's a more general question about just the effects of menthol in cigarettes. I think a lot of this, again, is something that the Committee is going to have to wrestle with a little bit, because we're all within the constraints of the statute.

As far as the public health piece, I think the critical questions there are the questions about any information about the impact on current users in terms of, you know, their ability to quit or not quit, or the likelihood of nonusers to start to use. Because in the statute that's the general provision -- when it talks about the public health or the population effect -- that is often referred to.

DR. SAMET: Okay. I think that these are probably two issues that the Committee will need to delve into a little bit as we have our discussion.

Considering, presumably, if a recommendation were made that menthol should be removed from cigarettes, or that menthol cigarettes should not be marketed, that that would extend to all menthol in all cigarettes, as opposed to mentholated cigarettes.

DR. HUSTEN: Well, I think -- you know, there are a variety of ways that it could go. It could be all menthol, or it could be more -- if it's enough to be a characterizing flavor.

DR. SAMET: Okay. I think we will probably need to learn more about this as we move forward.

Are there other clarifying questions, or perhaps nonclarifying questions?

Okay. Then, I think we have arrived 25 minutes early at break time. That said, I think let's stick to 15 minute break times. And I need to remind the Committee members that there should be no discussion of the meeting topic during the break amongst ourselves or with any members of the audience. So let's reconvene about five after 10:00. Thank you.

(Whereupon, a recess was taken.)

DR. SAMET: If I can ask everyone to be seated, please, we're going to move on. I think our 15 minutes is up.

Our next presenter is Dr. Ralph Caraballo from the CDC. He is epidemiology Branch Chief in the Office of Smoking and Health. He will be talking about the use of menthol cigarettes by demographic groups.

DR. CARABALLO: Thank you. Thank you to the Committee for the opportunity to discuss the epidemiology of menthol cigarette use in the United States. My name is Dr. Ralph Caraballo, Chief of the Epidemiology Branch in the Office on Smoking and Health, Centers for Disease Control and Prevention in Atlanta, Georgia.

Let me, before I start my presentation, say that the findings and conclusions in these presentation are mine, and do not necessarily represent the official position of the Center for Disease Control and Prevention.

Today I'm going to provide you with an

overview of the use of menthol cigarettes among various U.S. demographic groups. I will begin by describing two relevant publications and the main data source which I will be using.

Then I'm going to describe current patterns in menthol cigarettes use, first in terms of absolute numbers of menthol cigarette smokers; and then broken down by race, age, and gender.

Next, after briefly summarizing recent trends in overall cigarette use among U.S. adolescents and adults, I will describe trends in menthol cigarette use from 2004 to 2008 for adolescents and adults broken down by age, gender, and income, with age and gender analysis further broken down by racial/ethnic group. After recapping the major findings, I will conclude by briefly discussing limitations of the data on this topic.

I want to start by calling your attention to two recent publications on menthol use in the United States. These publications provide a good summary of demographic patterns of menthol cigarette use in this country and several methodological

issues relate to self-reporting of menthol cigarette use.

In 2004, Gary Giovino and colleagues published an overview of the demographics of menthol cigarette use in the United States. His analysis provided a detailed review of cigarette brand preferences and patterns of menthol cigarette use among youth and adults in the United States, drawing on data from the 2000 National Survey on Drug Use and Health, or NSDUH for short; and from 1998 to 2000, Monitoring the Future Survey.

However, much of the NSDUH data presented in this paper looked at the combined U.S. population age 12 years or older. In November of 2009, the U.S. Substance Abuse and Mental Health Services Administration, or SAMHSA, published a report on menthol cigarette use in this country drawing on 2004 to 2008 data from NSDUH.

Most of these publications are very good background resources on the demographics of menthol cigarette use in the United States and on available data sources.

In my presentation I will be focusing on the NSDUH as my primary data source. Even though other surveys, including the Monitoring the Future Survey, the National Youth Tobacco Survey, and the National Health and Nutrition Examination Survey collect some information on menthol cigarette use or on cigarette brand smoked by smokers, I chose to present data from the NSDUH survey because it has a larger sample size, which allows for more precise estimates of menthol cigarette use, and because it is a data source that captures information on menthol cigarette use for both adolescents and adults for racial/ethnic groups other than African Americans, Whites and Hispanics.

I will provide more recent and detailed data which expands on 2009 NSDUH report. In my presentation, when possible, I will present NSDUH data broken down by gender and race/ethnicity for adolescents age 12 to 17 years; young adults, age 18 to 25 years; and adults, age 26 years or older.

Before discussing the NSDUH data, I want to briefly describe the methods used in this survey,

and to share the wording of the question that it uses to assess menthol cigarette use.

The NSDUH provides nationally representative data. It is a household survey which collects information on the U.S. civilian, non-institutionalized population aged 12 years and older.

The NSDUH had more than 68,000 respondents in 2008. In terms of response rates, 89 percent of selected households completed the screener, with 74 percent of selected persons completing the interview. The surveys have similar sample sizes and response rates in 2004 through 2008.

The NSDUH includes two questions that are relevant to cigarette use. One question reads, were the cigarettes you smoked during the past 30 days menthol? Prior to 2004, this question was worded differently. As a result, we can only look at data for the years 2004 to 2008, which limits the number of data points we have available to track trends over time.

The NSDUH survey also asked about the

specific brand that respondents smoked in the past 30 days. However, we did not use that question to track menthol cigarette use, given that many leading cigarette brands have menthol and nonmenthol subbrands, and these details are not collected in the survey.

So now let's go to who is smoking in the United States -- who is smoking menthol cigarettes? How many Americans smoke menthol cigarettes?

On average, in each year, using NSDUH survey -- oh -- on average in each year, using the NSDUH survey, it is estimated that there were one point -- let me go back -- there were about 1.1 million adolescent menthol cigarette smokers aged 12 to 17 years in the United States in the combined years 2004 to 2008. It also estimated that, on average, there were about 18.1 million U.S. adult menthol cigarette smokers aged 18 years or older during those years.

Thus, combining these figures, the average total number of menthol cigarette smokers in the United States was approximately 19.2 million each

year over this period.

So now we turn to answering the question, who smoked menthol cigarettes in this country?

I want to start by examining patterns of menthol cigarettes use broken down by racial/ethnic group. I will look at this topic in two ways: First, in terms of the prevalence of menthol cigarette use within cigarette smokers of each racial and ethnic group; then, in terms of proportion of all cigarette smokers in the United States who belong to each racial or ethnic group.

In other words, in the first analysis the denominator will be all cigarette smokers, including both menthol and nonmenthol cigarette smokers within each racial/ethnic group; while in the second analysis, the denominator will be all menthol cigarette smokers in the United States.

One obvious and important finding is that African American smokers are far more likely to smoke menthol cigarettes than smokers of other U.S. racial or ethnic groups.

Among adolescents aged 12 to 17 years,

clear differences were observed among racial/ethnic groups in the proportion of menthol cigarette smokers among all cigarette smokers. About seven of ten African American smokers in this age group reported smoking menthol cigarettes, followed by about half of multi-race and Asian smokers.

Overall, the bar on the far right shows that almost half of adolescent smokers aged 12 to 17 years reported smoking menthol cigarettes in the past 30 days.

Clear differences among racial/ethnic groups in the proportion of menthol cigarette smokers among all cigarette smokers were also observed among adults. About eight of ten African American adult smokers reported smoking menthol cigarettes, followed by about half Native Hawaiian and other Pacific Islander adult smokers.

Again, looking at the bar to the far right, overall, about three of ten adult smokers reported smoking menthol cigarettes.

Now, we will turn to the second lens for looking at menthol cigarette use by racial/ethnic

groups. In this approach, the denominator is all U.S. menthol cigarette smokers. From this perspective, we see that even though African Americans have a very high prevalence of menthol cigarette use, Whites make up the majority of both adult and adolescent menthol cigarette smokers in the United States.

The pie chart on the left shows that members of minority racial/ethnic groups account for almost half of all adult menthol cigarette smokers. Still, the majority of adult menthol cigarette smokers are White, followed by a substantial proportion of African Americans and smaller proportions of Hispanics and other racial or ethnic groups.

The pie chart on the right show the distribution of adult smokers who reported smoking nonmenthol cigarettes. Whites make up about 80 percent of these smokers, followed by Hispanics and smaller proportions of African Americans, American Indians and Alaskan Natives, Native Hawaiians and other Pacific Islanders, Asians, and

others.

Among youth aged 12 to 17 years, we observed somewhat similar patterns as among adults.

The pie chart on the left shows smokers of menthol cigarettes aged 12 to 17 years broken down by racial/ethnic group. The pie chart on the right shows smokers in this same age group reported smoking nonmenthol cigarettes; again, disaggregated by racial/ethnic group.

As was the case among adults, a large majority of nonmenthol cigarette smokers are white, followed by African American, Hispanics, and other racial and ethnic groups.

Now, we will take a look at menthol cigarette use among all smokers broken down by age groups. The information I will present shows that proportionately adolescents are more likely to smoke menthol cigarettes than adult smokers.

For example, this slide from the 2009 SAMHSA report shows that younger smokers are more likely to smoke menthol cigarettes. A higher proportion of cigarette smokers smoke menthol

cigarettes among adolescents than among young adults or older adults. This inverse relation between age and smoking menthol cigarettes is statistically significant.

This graph shows that the proportion of menthol cigarette smokers among all cigarette smokers is higher among adolescent than among adults in most, but not all, racial or ethnic groups.

Among White, Hispanic, Asian, and multi-racial youth, the proportions of adolescent cigarette smokers reporting smoking menthol cigarettes are significantly higher than among adults. However, the proportion of African American adolescent cigarette smokers reporting smoking menthol cigarettes is significantly lower than the corresponding proportion for African American adult smokers. This observed difference requires additional study.

However, the most significant point here is that very high proportions of both African American adolescents and adult smokers smoke menthol cigarettes.

Turning now to gender, the scientific literature consistently shows that females are more likely to smoke menthol cigarettes than males, as illustrated by this slide from the SAMHSA report. This slide shows that this gender difference is present across racial/ethnic groups for respondents aged 12 years and older. A higher proportion of female smokers than male smokers smoke menthol cigarettes among African Americans, Whites and Hispanics.

The lack of a significant gender difference in the other racial/ethnic groups probably result from the lack of precision of the estimates for this populations due to small sample size.

Even with the NSDUH survey's relatively large sample size, when subdivided by race/ethnicity, the margins of error for these groups become larger, making it more difficult to detect statistically significant differences.

Next, I'm going to present data on overall trends in cigarette smoking prevalence among youth

and adults in the United States. Here I am going to talk about cigarette use in the U.S, thus, the denominator includes both smokers and nonsmokers.

These data will provide a backdrop for our discussion of trends in menthol cigarette use.

In general, cigarette smoking prevalence in this country has been declining for both adolescents and adults over the past ten to 15 years.

The Department of Health and Human Services uses the Youth Risk Behavior Survey as its data source to track cigarette smoking prevalence among 9th through 12th grade students for Healthy People 2010 objective 27-2b. Based on this survey, cigarette smoking among 9th through 12th grade students fell by 40 percent from 1997 to 2003; from 36.4 percent to 21.9 percent. This survey shows a point decline in smoking prevalence of 7.5 percent from 1991 to 2007. 2009 data from this survey will be available later this year.

The Department of Health and Human Services uses the National Health Interview Survey

to track U.S. adult cigarette smoking prevalence from Healthy People 2010, objective 27-1a. This survey shows that adult smoking prevalence fell significantly from 1998 to 2004, but has remained relatively unchanged since then. Even with population growth, this decline in smoking prevalence resulted in an estimated 1.2 million fewer U.S. adult smokers in 2008 than in 1998.

Now, we will discuss trends in menthol cigarette use for the period from 2004 to 2008. I will start by looking at trends by age. Here, and in the remainder of my presentation, I will once more be relying on data from the NSDUH.

I will present trend data for Africa Americans, Whites and Hispanics only. The reason that I am not looking at other racial groups here is that the annual numbers of respondents for these group are too small to yield precise estimates.

So I will begin with adolescents. The proportion of adolescents cigarette smokers smoking menthol cigarettes has increased significantly in recent years. Among all past-month smokers aged 12

to 17 years, the proportion of smokers of menthol cigarettes increased significantly from 43.4 percent in 2004 to 48.3 percent in 2008, for an 11 percent increase over four years.

This increase in the proportion of adolescent cigarette smokers who smoke menthol cigarettes reflects an increase in menthol cigarette youth among White adolescents, represented by the blue line, who were the only racial/ethnic group to show a significant increase over this period.

Now, we will turn to trends among adults. An overall increase in past-month menthol cigarette use was also observed for adults. Because there are many more adult smokers than adolescent smokers, the estimates for adults are more statistically precise than those for adolescents. As a result, a smaller point prevalence difference is more likely to be statistically significant for adults than for adolescents.

This graph shows a slight, but significant increase in the proportion of menthol cigarette smokers among all past-month adult smokers. This

proportion increase from 30.2 percent in 2004 to 33.8 percent in 2008, for a 13 percent increase over four years. This compared to the 11 percent significant increase in this proportion observed among adolescents during the same period.

These increases occurred in a period when the overall prevalence of cigarette smoking among adolescents was slowly declining, while adult smoking prevalence has been stagnant over the last few years.

Based on the NSDUH data, the proportion of all adult cigarettes smokers aged 18 to 25 years who smoked menthol cigarettes, represented by the dark blue line, increased from 34.1 percent in 2004 to 40.3 percent in 2008, for a significant 17 percent increase.

The proportion of adult smokers, aged 26 years and older who smoked menthol cigarettes, represented by the light blue line, increased from 29.1 percent in 2004 to 32.2 percent in 2008, for a borderline significant increase of 10 percent.

Next, I will review the data on trends in

menthol cigarette use by gender. The NSDUH report shows that the proportion of male cigarette smokers aged 12 years or older who smoked menthol cigarettes increased significantly from 26.9 percent in 2004 to 30.8 percent in 2008. The proportion of female cigarette smokers in this age range who smoked menthol cigarettes increased from 35.9 percent in 2004 to 37.5 percent in 2008, a nonsignificant increase.

Significant increases in past-month menthol cigarette use were observed among White and Hispanic male smokers, aged 18 and older from 2004 to 2008, according to NSDUH data. The proportion of all White adult male past-month cigarette smokers who smoked menthol cigarettes, represented by the light blue line, increased significantly from 18.5 percent in 2004 to 21 percent in 2008.

The proportion of all Hispanic adult male past-month cigarette smokers who smoked menthol cigarettes, represented by the green line, increased significantly from 22.7 percent in 2004 to 29.5 percent in 2008.

In contrast, the proportion of African American adult male past-month cigarette smokers who smoked menthol cigarettes, represented by the purple line, did not change significantly, standing at 83 percent in both 2004 and 2008. However, it is important to note that this proportion was already very high in 2004, potentially creating a ceiling effect.

In contrast, among adult women, no significant changes were observed in the proportion of African American, White, or Hispanic past-month cigarette smokers who smoked menthol cigarettes during this period.

This proportion increased non-significantly from 86.3 percent in 2004 to 91.9 percent in 2008 among African American adult female cigarette smokers.

Again, as with African American men, it is important to note that this proportion was already very high in 2004.

Nonsignificant increases from 38.9 percent to 41.4 percent, and from 26.7 percent to

28.9 percent in this proportion were observed for Hispanic and White women, respectively, over this period. Even though nonsignificant, these trends point to potential increases in the near future.

Finally, increases were also observed during 2004 to 2008 period in the proportion of adult smokers who smoke menthol cigarettes among certain specific family income brackets. Specifically increases in this proportion were observed among respondents with family incomes between $20,000 and $49,999, and with incomes of $75,000 or more, represented by the blue and orange lines respectively.

It is also important to note that respondents with family incomes below 50 percent, represented by the blue and green lines, were proportionally more likely to smoke menthol cigarettes than respondents with higher family incomes.

Thus, to summarize, during 2004 to 2008 in terms of overall absolute numbers, we saw that 1.1 million adolescents smoked menthol cigarettes; that

18.1 million adults smoked menthol cigarettes; and that a total of 19.2 million Americans smoked menthol cigarettes.

In terms of racial or ethnic group, we observed that almost half of adult menthol cigarette smokers came from minority racial/ethnic groups. That the great majority of African American adolescents and adult cigarette smokers smoked menthol cigarettes; and that the proportion of cigarette smokers who smoke menthol cigarettes increased significantly from 2004 to 2008 among White adolescents, White men, and Hispanic men. And Whites made up the majority of U.S. menthol cigarette smokers.

In terms of age, almost half of adolescent cigarette smokers smoke menthol cigarettes. Three of ten adult cigarettes smokers smoke menthol cigarettes. Younger smokers were more likely to smoke menthol cigarettes. And from 2004 to 2008, the proportion of menthol cigarette smokers among all cigarette smokers increased in each of the three age groups considered; 12 to 17 years; 18 to 25

years, and 26 years or older.

In terms of gender, we saw that female smokers were more likely to smoke menthol cigarettes than male smokers. That the proportion of cigarette smokers who smoked menthol cigarettes increased significantly among males aged 12 years or older, but not among -- but not among their female counterparts.

In terms of income, we saw that adult smokers with family incomes of less than $50,000 were more likely to smoke menthol cigarettes than adult smokers with higher family incomes. That the proportion of adult cigarette smokers who smoke menthol cigarettes increased significantly among adult smokers with family incomes between $25,000 and $49,999; and that the proportion of adult cigarette smokers who smoked menthol cigarettes also increased significantly among adult smokers with family incomes of $75,000 or more.

I want to conclude by talking briefly about the limitations of the data that this analysis is based on. One issue that has been discussed in

the scientific literature is that both youth and adult smokers may under-report menthol cigarette use.

For example, the 2004 paper by Giovino and colleagues I cited earlier, which examined this issue using NSDUH data from 2000, when the NSDUH menthol cigarette question was worded differently, found that among all smokers aged 12 years and older, 7.9 percent of respondents who reported smoking a primarily menthol cigarette brand like Newport, Kool, or Salem also reported in the question about menthol cigarette use that they did not smoke a menthol cigarette.

In this paper they also found that 4.2 percent of respondents who reported smoking a cigarette brand like Winston, that is only available in non-menthol form, also reported in the question about menthol cigarette use that they did smoke a menthol cigarette.

The same paper by Giovino and colleagues also mentioned that these discrepancies in self-reported menthol cigarette use were higher for

adolescent smokers aged 12 to 17 years than for adult smokers; although, they did not provide specific data on this issue. However, this issue should not impact the trend analysis I have presented.

Another limitation of this analysis the NSDUH data I have presented come from annual cross-sectional surveys. While the NSDUH survey provides a good picture of the demographic of menthol cigarette use, we are currently unable to perform confirmatory analysis using cigarette brand information from other surveys.

So this concludes my presentation. Thank you very much.

DR. SAMET: Okay. Thank you, Dr. Caraballo.

What we are going to do now is move on to the presentation by Dr. Deirdre Lawrence on Menthol Sensory Qualities and Topography. The audience, I believe, does not yet have the copy of the slides, which will be on the main table outside.

Dr. Lawrence, thank you.

DR. LAWRENCE: Hello. My name is Dr. Deirdre Lawrence, and I'm an epidemiologist at the National Cancer Institute, a tobacco control research branch. I am currently on detail at FDA's new Center for Tobacco Products. This is the first of several presentations summarizing the published scientific literature.

Today, I will tell you about the literature on menthol sensory properties, and its possible effects on smoking topography. So your first question might be, what is topography? What I mean by this is it's a -- it's a quantifiable component of smoking behavior often referred to as puffing behavior. The most commonly used measures in the literature included the number of puffs per cigarettes, and the puff volume, often reported as molliers. Other measures included puff duration, puff flow, and interpuff intervals.

This slide demonstrate some instruments that have been used to actually measure topography. As you can see on the top right, as well as on the right-hand side, these are desk-top instruments that

can be used in a laboratory setting where the smoker -- I'm going to try to use a pointer here -- maybe not -- where the cigarette is -- of choice is inserted into the device, and the smoker is able to smoke; and the machine actually captures the puff profile.

On the bottom left corner, you will see a handheld portable device where the cigarette is smoked in a more naturalistic environment, and the measurements are recorded.

This is a screen shot of what the puff profile might look like. It shows you the number of puffs; the puff volume, which is the area under the curve; the puff duration over time, as well as the interpuff intervals.

We are post literature. There are three main research questions that we were trying to answer. One is, what are the properties or the sensory properties related to menthol? How do these properties actually contribute to the experience of smoking? And do these properties actually alter the smoking behavior for the smoking topography?

You have heard mentioned earlier today about the NCI bibliography, and I brought a copy here so you can actually see what it looks like. I was one of the team members responsible for putting together this bibliography, and it's available on the NCI web site, and it serves as a resource. It has 343 abstracts related to menthol and tobacco; and I believe there is a question about the search terms. And on Roman numeral page five it describes what the search terms were.

We used several databases, including Pub Med, Scopist, as well as the Web of Knowledge. The search terms included menthol cigarettes, mentholated cigarettes, menthol tobacco, mentholated tobacco, menthol smokers, and menthol; and several terms related to disease and health. And there is a long list -- I won't read them all -- but terms such as addiction, nicotine, marketing, cancer, biomarkers, environmental tobacco smoke, et cetera.

I will be happy to answer any questions later about this methodology.

This was used as a basis for us to get

started in terms of summarizing the scientific literature around menthol. The search was done up until mid-January -- sorry -- the middle of 2009. So at FDA when we decided to take this on, we actually updated the bibliography by using the same research terms and identified some additional articles using the same methodology. So those were included in these presentations, as well as the White papers that we were developing around the literature.

For this presentation and -- for most of them, actually -- the review articles were quite helpful in terms of providing background information and providing additional sources for research articles we might have missed in our search; but we primarily focused on the primary research articles. And for this presentation 26 articles were relevant to sensory properties in topography.

For the ease of the presentation here, I have just displayed several of the reviews that have been published about menthol's pharmacology and sensory qualities. There are only a few published

topography studies; six to be exact. And there is a great deal of variability between these studies.

For example, the study design varies from study to study. Some employed -- in some studies the smokers smoked both menthol and nonmenthol cigarettes, which is sometimes referred to as cross-over studies. And other studies the smokers actually smoked their preferred brand, their preferred cigarette.

There are also differences in how the smokers were asked to smoke. Some smokers smoked ad libitum, or as they normally would; whereas, others had to follow a rapid smoking procedure where they had to take puffs every 15 seconds. This was to control for variability between puffs. And only one study actually varied the nicotine -- I'm sorry, the menthol content to see if there was an effect on topography. So as a result, a comparison was difficult between the studies, but I will show you what we have found.

First of all, what are the sensory properties of menthol? One is flavor or taste.

Menthol is naturally found in peppermint oil or cornmint oil, and it stimulates the olfactory and taste receptors, and seems to be known for its characteristic mint flavor and smell.

In a baseline questionnaire among menthol smokers, 60 percent responded that they would pay more money for a menthol cigarette than for a nonmenthol cigarette. This could suggest that flavor or taste may play a role. They also gave taste as one of the three main reasons for smoking menthol cigarettes.

One of the most well-known properties associated with menthol includes the sensation -- the cooling sensation that's often felt. When menthol is applied to the skin or mucosal surface it causes a sensation of cool or warm, which is attributed to the stimulation of thermal receptors. Menthol's affect on temperature sensation is likely mediated through a family of channels -- or family of proteins caused the transient receptor potential, or TRP. Menthol actually activates the TRP 8, the cold activated receptor; as well as TRP 3, the warm

activated receptor.

It's important to note that this sensation of cold or warmth is determined by the activity of the thermal receptors on the skin and mucosal surface, not by actual change in temperature.

These receptors are found in the upper respiratory track, the nose and larynx; and menthol delivery contributes to the sensory receptors in the mouth and throat. Menthol emulations stimulate trigeminal cold receptors resulting in a cooling sensation without a change of physiological temperature, as I said earlier. And menthol can both increase the sensation of cold in the oral cavity; menthol also enhance or attenuate feelings of warmth.

Menthol effects on respiration seem to be complex, and not as well understood. Menthol has been used as a decongestant. And studies show that subjects exposed to menthol report a perceptive of increased nasal air flow. However, objective measurements do not actually show physical decongestant activity or any changes in airway

resistance.

In animal experiments menthol inhibited ventilation, or the drive to breathe, and could increase breath hold time in humans. Menthol can act as a cough suppressant; and additional animal studies show that menthol could reduce mucous clearance in bronchial dilation.

Menthol has both an analgesic, also known as pain killing, as well as anesthetic properties resulting in a reversible loss of sensation. Several mechanisms have been proposed for menthol's analgesic effects, such as the TRP receptors that I mentioned earlier; as well as the activation of the kappa opioid system. Again, these are proposed mechanisms.

Menthol is an irritant, but tolerance can be developed after repeated exposure. In addition, it's been shown that nicotine can actually reduce the irritant properties of nicotine -- menthol can reduce the nicotine's -- let me slow down. In addition, it's been shown that menthol can reduce nicotine's irritant properties.

Perceived strength is complex like taste, and is derived through a variety of factors like irritants, temperature, and taste. Menthol can produce a varying degree of irritation and changes in temperature perceptions. It's important to note that irritation may not necessarily be bad. For example, spicy food may be considered an irritant by some, but liked by others.

The studies -- there was a study that showed that cigarettes with descriptors indicative of lower machine derived tar yields -- that is ultra light or light -- had more menthol and higher rates of menthol to tobacco than other cigarettes. Ultra light cigarettes have greater amounts than mild or nonmenthol flavored cigarettes.

The author proposed that menthol may be used to offset production in smoke delivery, or perceived strength in low yield cigarettes.

In a separate study, menthol smokers reported that menthol cigarettes are more soothing to the throat than nonmenthol cigarettes.

Now, I will describe some of the published

findings that have analyzed publicly available tobacco industry documents.

In a review -- a published review of publicly available documents, Kreslake and colleagues showed that the tobacco industry developed different kinds of products with different levels of menthol. One was a low content menthol cigarette thought to mask the taste of tobacco and reduce throat scratch.

The other category had a higher menthol content for increased perceived strength in menthol flavor. And it was stated that these might be for those who seek out the specific menthol flavor and associated physical sensation.

This study also showed that smoking status was associated with the overall liking of menthol concentrations with heavy smokers preferring higher levels of menthol, and moderate smokers preferring moderate levels.

Wayne and Connolly published a study analyzing the publicly available tobacco industry documents to assess tobacco industry research on the

sensory properties of menthol, and the proposed possible uses as identified in tobacco industry documents.

I actually borrowed their table four, simplifying it slightly for ease of presentation. And as you can see, it describes menthol's properties that were also identified in the scientific literature, such as cooling, anesthetic or analgesic effect, impact or perceived strength, as well as sensory.

We see that there are similar properties reported for menthol in both the published scientific literature, as well as published analyses of the publicly available tobacco industry documents.

These properties include cooling sensation of ease of respiration, flavor, et cetera. It's proposed that these properties could result in larger puff volumes, increased frequency, or number of puffs per cigarette, greater intensity of smoking, et cetera; or that the inhalation patterns could be altered due to increased breath hold time.

So the question is, what do the studies tell us?

There were six comparative studies examining whether there is increased puff volume or puff frequency associated with menthol cigarettes versus nonmenthol cigarettes. These were all done in the 1990's. The first four studies were all men. Three of the four through -- I'm sorry -- drew their sample from inpatients undergoing treatment for drug and alcohol dependence.

They employed a cross over design where menthol and non-menthol smokers participated in a rapid smoking procedure, which, again, this was a controlled smoking procedure, taking puffs every 15 or 30 seconds. In one session the smokers smoked menthol cigarettes. In a separate session the smokers smoked non-menthol cigarettes.

In the study done by Dr. Jarvik, the subjects were recruited from the community; and smokers were able to smoke as they normally would, instead of using the rapid smoking methodology.

The two later studies were done among

women only, and they were women from the community; and they were able to smoke as they normally would.

The hypothesis was that smokers smoking menthol cigarettes would have a higher puff volume than smoking -- than smoking non-menthol cigarettes.

However, one study showed that menthol significantly increases the puff volume. In the 1996 Ahijevych study it reported the higher volume, but it was not significant.

The McCarthy study reported that study participants inhaled almost 40 percent more smoke when smoking nonmenthol cigarettes than when smoking menthol cigarettes.

Again, with puff frequency or number of puffs per cigarette, authors hypothesized that because of menthol cooling and anesthetic effects, smokers would take more puffs from menthol cigarettes, than from nonmenthol cigarettes.

Two of the studies showed fewer puffs per cigarette for menthol cigarettes; and three of the studies found no significant effect for the menthol cigarettes.

Puff volume and number of puffs were the most frequently used measures of topography; but there were a few others that were reported. I just wanted to let you know about them.

For example, in Dr. Jarvik's study, as I reported earlier, it was found that there was decreased puff volume and few puff numbers per cigarette among menthol smokers; but the puff flow rate was significantly lower during menthol cigarette smoking. There were no significant differences in the other measures, such as puff flow and puff duration.

In the Ahijevych study amongst women, it was found, again, that larger puff volumes among menthol smokers; but there were no significant difference in the other measures, such as puff duration and interpuff interval.

I spent most of the time describing topography as being a quantifiable measure. Some of the studies did have self-reported topography. In a perspective study menthol and nonmenthol smokers reported similar puff numbers for cigarettes, depth

of inhalation, and length of cigarette smoke.

Similarly, in a separate study, subjective rating of harshness did not differ between menthol and nonmenthol smokers. However, one study did report that menthol smokers felt they could inhale from menthol cigarettes more easily and deeply than nonmenthol cigarettes. So the self-reported measures are not consistent.

There are few limitations to keep in mind when examining the results from these studies. One is that they all had small sample sizes with the exception of one study, which contained 95 participants. Most had less than 40.

There were not a large enough sample size to allow for inter and intra individual differences in smoking behavior. Most were gender specific.

Puffing topography among men yielded smaller volumes of menthol cigarettes; whereas, among women, there was no significant difference noted in one study, and larger puff volumes were described in the larger study. The results may not be generalizable, because the subjects were drawn --

well, three of them were drawn from drug and alcohol treatment centers.

In summary, the sensory properties of menthol have been well-documented and include flavor, cooling and warming, respiratory, and analgesic effects. Also, the key component in the perceived strength of the cigarette. Because of these properties many researchers have hypothesized that menthol may alter topography by way of increased breath holding, large inhaled volume, et cetera; but the effects on topography are inclusive.

For puff volume most of the studies showed a depressive effects or no effect. The larger study, which was among women only, showed an increase in puff volume among menthol smokers.

For puff number per cigarette three studies showed fewer puffs among menthol studies, and three showed no effect. No effect was found when menthol content was varied, and self-report assessments were not consistent.

Thank you.

DR. SAMET: Okay. Thank you.

I think we're going to take the opportunity being ahead of schedule to have clarifying questions now, I think, actually -- don't go away -- on both of these presentations.

So Ralph, if you could come up as well; and we can move through questions on both of these presentations, I think that will fit together just fine.

So questions from the Panel. Melanie.

DR. WAKEFIELD: Thanks, Ralph, for a very interesting presentation.

I know that there is data on smoking prevalence from the Monitoring the Future Surveys, as well as teenagers. I'm not sure whether that data includes menthol consumption.

DR. CARABALLO: No, they have the brand only -- you know, what brand of cigarette they smoke.

DR. WAKEFIELD: Right. Just your comment at the end, you were unable to perform confirmatory analysis with other data sets. Does that mean that you couldn't access other data sets, or that you did

access it and --

DR. CARABALLO: Well, we were able to access other data sets. We looked at NHANES, Monitoring The Future, et cetera. The problem is that no survey that I know about collects information both self-reported and then something that is confirmatory like the bar codes on the side of the cigarettes, or even the picture of the specific brands, so we know exactly what they smoke. That's not available.

DR. WAKEFIELD: So what you are saying is the data that you used is the best data to really look at this question of what's going on?

DR. CARABALLO: Yes, in terms of sample size and racial/ethnic groups having enough of them; yes.

DR. SAMET: Neal.

DR. BENOWITZ: One of the things that was most striking to me was the difference in the prevalence of menthol smoking amongst adolescents versus adults. The question is, are there any data that would allow us to sort out whether this is a

cohort effect, or whether this is a time shift?

In other words, do adolescents start to smoke menthol cigarettes, and then switch to other cigarettes for the most part? Or are adolescent in the last ten years different than adolescents ten years before that?

DR. CARABALLO: Yes. Excellent question.

All data that is out there -- at least that I'm aware of -- are cross sectional in nature. The ones that -- the few surveys that collect menthol information are cross-sectional in nature.

I know that Dr. Joshua Rising is presenting in initiation, and with cross-sectional data -- I'm not going to give, you know, his presentation or his results -- but with cross-sectional data, he was able to look at those who reported start smoking in the last year, as opposed to more than a year.

However, that doesn't answer your question of the switching part. There is no data that I know about that have that kind of information. The prospective data that you can follow the case and

know if they're switching from menthol to nonmenthol or vice versa.

DR. SAMET: Jack. Jack.

DR. HENNINGFIELD: Thank you. I have a question for each of you.

Dr. Caraballo, this goes back to something Dr. Samet mentioned earlier, and that is the cigarettes -- a lot of cigarettes contain menthol. I guess by convention when you are talking about menthol cigarettes, you are talking about cigarettes that are branded, marketed; and I guess the way I look at it is, or otherwise characterized as menthol. People are self-reporting, so they have got to know on the basis of the branding, marketing, or characterizing.

DR. CARABALLO: Correct.

DR. HENNINGFIELD: Do we have any evidence that -- or population or individual effects on menthol levels that are not branded or characterized? In other words, cigarettes containing menthol versus those that do not contain menthol in that category of cigarettes that are not

characterized as menthol.

DR. CARABALLO: I'm not sure I follow the whole question -- what specifically is your question?

DR. HENNINGFIELD: So we have a category of -- we have cigarettes that are not branded as menthol; some of which contain menthol and some of which don't.

DR. CARABALLO: Right.

DR. HENNINGFIELD: Do we have any population data to separate smokers of those two categories of cigarettes?

DR. CARABALLO: Hum. We will have to look at the specific brands. I know that Celebuki has done some studies on that. The only data set that I'm aware of that have specific data only for adults, 20 years or older, is the NHANES. They collect the side -- the bar code on the side of cigarette packs, so you will know exactly what brand of cigarettes this person smoke.

Now, in terms of what is the menthol level in cigarettes that, let's say, they are not labeled

as menthol, but they still have some menthol in them and trying to analyze that data, I think that it is possible to do that.

I know that NHANES have a problem in the sense that sample size they collect information in a two years basis, so they aggregated the data that they collect from two years, and still the number of smokers that you have is not enough. Obviously, when you start disaggregating by specific brands, you know, then the numbers become smaller and smaller.

So I know what you are saying. No one that I know other than Celebuki has published some articles about that, but I don't know if anyone has done that kind of analysis or even if it's feasible to do it at the present time.

DR. HENNINGFIELD: So in principal if we were able to identify either on the basis of public information or information requested from the tobacco industry as to what brands have what levels, in principal, would be possible to do such analyses.

DR. CARABALLO: I think so, yes.

DR. HENNINGFIELD: For other speakers, this is something I'm going to be coming back to, because I think one of the things I'm trying to sort out is any level of menthol versus characterizing branded or marketed.

And not completely unrelated, I have a question for Dr. Lawrence. This gets into -- and this is a question I will also have for other speakers, because we're going to be learning a lot about the effects of menthol -- or apparent effects on initiation, dependence, development, cessation. You have been talking about physiological and behavioral effects, sensory effects.

So in all of those areas what I'm trying to figure out is what information we have on dose response thresholds. When I mean dose response, it is either the total content of menthol, or perhaps the concentration of menthol that is in the cigarettes. And this, obviously -- I think, obviously, gets to issues if you are going to try to think about a performance standard, what would it look like? Is there any basis for limitations based

on evidence of menthol dose effects? So in all the work that you have looked at, what do we -- what can you conclude, if anything, about menthol dose-response effects?

DR. LAWRENCE: I cannot conclude anything about menthol dose response, unfortunately. Only one of the studies that I found actually varied the dose of menthol, and found no effect in terms of topography. Dr. Hoffman is going to be talking later today about the health effects that were provided; but I don't know if there is anything about dose response there either.

DR. HENNINGFIELD: Well, I was -- because I was intrigued by the difference -- apparent preferences in tenured smokers versus moderate. So there must be something. And I wonder if there is another area were if, on the basis of your analysis, there may be information in the literature, in the documents, or if this is another area were we may need to turn to the industry which adds menthol to find out what the basis is for how much is added.

DR. LAWRENCE: Yeah, I think you are

right. We can go back and look at the literature; maybe we missed something. But I think you are right, they're other sources of information; and perhaps, the industry can provide some good information around that.

DR. SAMET: Patricia.

DR. NEZ HENDERSON: I have two questions. One for Dr. Caraballo and one for Dr. Lawrence.

Dr. Caraballo, in terms of age of initiation we know that in many of the studies that African Americans actually have later age of initiation. Do we have any data that will break it down by age of initiation in terms of menthol use -- menthol cigarette use?

DR. CARABALLO: That would be Dr. Rising, again, presentation. He is going to look at initiation. In terms of data available, in terms of age of initiation, yeah, it can be done with NSDUH data. And he is going to be presenting one side about that. You know, at what -- well, I'm not sure it was age. It's at least those who started -- let me clarify that; I don't think it's age. But he is

going to be presenting those who started smoking less than a year ago.

In terms of age of initiation, information is there, because they collect age information. And they collect if, at the present time, in the past 30 days, they are smoking menthol.

What they do not have is when they started smoking, they started smoking with menthol cigarettes, which is the same question that Dr. Henningfield was asking about; what are they smoking? Are they switching or not switching?

DR. NEZ HENDERSON: Then for Dr. Lawrence, do we have any data about topography among use and Africa Americans?

DR. LAWRENCE: Yes. Yes. We do have some information about topography among Africa Americans; but they didn't necessarily compare menthol versus nonmenthol. That was the challenge. And for adolescents there was one study that looked at adolescents. It was all menthol smokers. They were trying to examine racial/ethnic differences; and they found no racial/ethnic differences in terms of

topography. Because they didn't compare menthol with nonmenthol, we didn't necessarily include it here; but, perhaps, we should include it in the White Paper.

DR. SAMET: Okay. Dan.

DR. HECK: We have touched on so many topics already here almost simultaneously, it is already getting difficult with these interdictionary topics.

I think, Dr. Caraballo, with updating for some statistical analysis, the NSDUH report figures that we did, I think, integrate in just last fall; and to -- and also, I appreciate your pointing out the difficulty we have in distinguishing, you know, smoking initiation among youth from the brand preference reporting. And I wonder do you feel that the revised question now in the NSDUH survey regarding menthol, does it help to get at any of the ambiguity that Dr. Giovino pointed out in 2004 in terms of is there stability to use brands choice, or is there an instability in menthol preference or menthol identification? As a result of that,

perhaps, they can't buy cigarettes legally and are obtaining them where they can.

DR. CARABALLO: Well, obviously, I haven't looked at it in terms from the data analysis point; but if you are asking me about my opinion --

DR. HECK: Yes.

DR. CARABALLO: -- I think that it is an improvement from the question that was used before, because before -- some of the kids seem to have a problem, especially talking about youth 12 to 17. They were having some confusion between -- the way that the question was worded, you know. Do you smoke menthol cigarettes or regulars? And they were not clear between one and the other; and now the regular part of the question was deleted.

Information, not from NSDUH, but from other research I have performed in terms of trajectories of cigarette smoking, when we are talking about adolescents 12 to 17 who responded to having smoked in the past 30 days, you are going to have kids who smoke -- a proportion of them smoke everyday. Some of them are occasional smokers.

Some of them are in the trend stage and the experimental stage. So you have a cluster, an aggregate of kids who are in different -- different stages in their smoking.

For kids who haven't achieved daily smoking -- or depends on where in the occasional smoking they are. If they are just starting trying experimenting, I would think that it's more difficult for them to remember exactly what brand of cigarettes they smoke in the past 30 days. If they are bumming cigarettes. If they are, you know -- if they are still not allowed, or they don't go to a store and buy the cigarettes themselves. So there is always going to be some degree of misreporting.

DR. HECK: Yes.

And partially to address what -- Jack Henningfield's comment and something that Dr. Lawrence mentioned. As we anticipated we might, we have this situation where internal industry documents have been discussed in published work. So some of this information, such as Jack talked about, might be more appropriate to come out at subsequent

meetings.

But there are -- I will just offer that there are reasons -- you know, very pragmatic, technical reasons on a -- for instance, the menthol level in some of the lower yielding products is higher. That's simply because the strategies used to achieve lower smoke yields like filter ventilation, filter efficiency, paper verosity tend to reduce the menthol delivery more efficiently than some of the tar measures. So that a higher level of menthol is required to achieve a similar effect.

DR. SAMET: Thanks. Next, John.

DR. LAUTERBACH: I just want to point out one thing, is that many nonmenthol smokers would find any --

DR. SAMET: Clarifying question or --

DR. LAUTERBACH: Yes. Well, just a clarifying point about the -- the question what level or so is -- on Dr. Henningfield's question about menthol versus no menthol versus different levels. Maybe I need to rephrase the question asking Dr. Henningfield what he meant by that.

DR. SAMET: Well, we're actually, at this point, asking clarifying questions for our speakers.

DR. LAUTERBACH: Well, then, I guess the question would be, do we consider all menthol cigarettes the same?

DR. SAMET: Do either of you want to address that question?

DR. CARABALLO: Okay. Are all of them the same? I guess that depends in what we are talking about. You know, same in terms of what?

Are they the same in terms of exposure in the levels of the blood? Well, you know, I don't know to what degree we can talk in here things that have not been published, but we have a paper through clearance right now in which we compare self-reported menthol cigarettes and cotinine levels in the blood taking into account height, weight, race, ethnicity divided by -- because we know that there are differences in metabolism between African Americans and elimination.

We found no difference in terms of exposure between menthol cigarettes and nonmenthol

cigarettes. That's only one study. It has not been published; so it has to be peer reviewed, obviously.

So I guess that depends on if they are similar or different in terms of what? In disease, causing disease; in terms of causing to smoke. So it will be -- need to be clarified further.

DR. SAMET: Ursula.

DR. BAUER: Ralph, I'm interested in the apparent increase in use of menthol cigarettes over time; and I have two questions. One, what do we know about the availability or number of brands of menthol cigarettes changing over time? Was there more availability?

And the second question is, looking specifically at the 26 and older group -- so that's a group were brand preference is more or less firm. Are you hypothesizing that in that 26 and older group smokers are switching to menthol to account for that little up tick, or is the pool shrinking, but not shrinking evenly across the different --

DR. CARABALLO: If you look at cross-sectional data -- and it depends on which

group we're talking about. If you look at cross-sectional data, again, ideally the best thing will be to have prospective data to know what exactly is happening; but the pool of menthol users, you know, proportionally -- proportionally seems to be shrinking.

Numerically, it's increasing. Obviously, the pool of kids smoking up to 17, numerically, is much smaller than the group of 26 to whatever, 80 or 90. So numerically, there is a lot more menthol smokers in the 26 older. Proportionally, as we saw in the graph there, we see that proportionally there are more menthol smokers in the younger groups.

DR. BAUER: What I'm asking is, in that 26 and older age group, are you suggesting that among those smokers to account for that up tick in menthol smoking --

DR. CARABALLO: Oh, I see what you are saying.

DR. BAUER: -- people are switching to menthol, or is the pool of total smokers declining, but menthol smokers are not declining?

DR. CARABALLO: I would be guessing, obviously, here knowing that most initiation happens up to age 18 or 21. So by age 26 people have already started smoking at younger ages. If that pool is increasing in terms of menthol cigarette use, I would assume that what that means is that the pool from nonmenthol is decreasing. That people, as you are saying, probably are switching; but that's just an hypothesis.

DR. SAMET: Greg.

DR. CONNOLLY: Ralph, just to clarify Jack's question on brand use. Your presentation indicates that there is an inability to report brand use by age with the NSDUH Survey. Is that correct?

DR. CARABALLO: No. What I meant was that with the NSDUH we didn't use the brand information because some brands, as you know, can be either menthol or nonmenthol. We will have to replicate what Gary Giovino did and only look at brands that are only menthol; Newport, Kool, Salem; or brands that are only nonmenthol, and cross tabulate it with what was their response in terms of do you smoke a

menthol cigarette or not. We have not been able to do that.

In terms of only using brands for analysis, those brands that have both, you know, menthol and nonmenthol, we will not know the answer of what kind of cigarettes they smoke.

DR. CONNOLLY: Do you think it's worthwhile to sort, let's say for the younger age group, brands that we know that are mentholated or not mentholated?

DR. CARABALLO: Well, we know that -- we know that kids, adolescents basically smoke the most advertised brands. So if we do that kind of analysis, probably we are going to capture the vast majority of them in terms of menthol use and nonmenthol use.

DR. CONNOLLY: Let's look at a brand like Newport versus Kool. Those are two dedicated mentholated brands, where there is not misunderstanding. Can we sort for the younger age group differences in use between a Newport and a Kool?

DR. CARABALLO: I believe so. If numbers -- I don't know what the sample size for both of them are; but we are talking about, you know, starting with 68,000. And also data can be aggregated over a number of years, 2004 to 2008, because the questions were the same. So I believe that yes. The answer is yes, it can be done.

DR. CONNOLLY: I think that would be helpful for the Committee.

Second question is -- this is just a clarifying question. From 2004 to 2008, the sampling design didn't change in that survey.

DR. CARABALLO: Correct.

DR. CONNOLLY: So we feel comfortable, even though it's cross-sectional, that's not a limitation in that particular survey.

Then, Deirdre, in your presentation of the human studies, do they control for tar and nicotine levels in those cigarettes -- or nicotine levels, do you know?

DR. LAWRENCE: I don't know. I don't think so, but I don't know.

DR. CONNOLLY: And did the studies compute total volume of smoke received by one cigarette? Even though the puff may be larger the frequency is altered, the total volume from that cigarette may be altered or the number of cigarettes smoked per day.

DR. LAWRENCE: Yes. They took the total volume for the cigarette. And for some of the studies they took the average -- if they smoked multiple cigarettes, they took the average total volume for that cigarette -- per cigarette.

DR. CONNOLLY: Okay. I mean, I think to Jack's point, it would be very helpful for the Committee to have data that looks at actual menthol content; and to the extent that the staff could look at brands by menthol content, would it be in the raw tobacco or in the smoke. I think that would be helpful in the deliberation in trying to link together the two data things. Thank you.

DR. SAMET: Okay. Mark.

DR. CARABALLO: Can I say something?

I guess it's more in terms of follow-up of what Dr. Connolly just said. It's a question. Do

menthol concentration per specific brands may vary year per year, or is it kind of constant so it doesn't matter?

DR. SAMET: I think we will leave that as a question to pose that it may be the kind of question that we want follow-up information on. Mark.

DR. CLANTON: You know, what's really clear is that it appears that menthol, through it's neurosensory impacts has a lot to do with sort of the preference for a particular brand. It has a lot to do with maybe even some persistence of a particular brand; but it isn't clear, based on the data, that menthol and menthol content has much to do with persistence in terms of wanting to smoke over and over again.

So my question is, are there studies that are either planned or in the literature that are looking at menthol nicotine as a system complex? Because we know what effect nicotine has in terms of persistence. Menthol may actually have more to do with initiation than persistence. So are there any

studies planned on looking at them together?

Obviously, you can increase those levels of each; but are there any studies looking at maybe the two together?

DR. LAWRENCE: Not that I'm aware of. You made me think of two studies that were done on denicotinized cigarettes; but I can't remember the results right now. So that's an important question for us to take a look at. Thank you.

DR. SAMET: Jack, we are back to you.

DR. HENNINGFIELD: Thank you. What I'm trying to sort out with my question is what information you have that you think may be available. What information we may be able to get from other speakers, and what we may need from the industry.

So here is a really basic one. In your opening, talking about sources of menthol was a reminder to me, what do we mean by menthol? Whenever we talk about menthol, is it a single molecular entity, or is it a category of substances that -- where the term "menthol" is rather loosely

applied?

I know there are menthol analogues; there are other substances. Is it just a singular molecular entity that is used in all cigarettes, do we know?

DR. LAWRENCE: You asked a very important question. And the menthol -- to answer your question, for the studies that we analyzed for this particular presentation menthol was applied both in the natural -- in it's natural form, peppermint oil, cornmint oil; but there are also studies that used synthetic menthol.

In terms of is it a family or class of compounds, that's a good question. There are different variations of menthol, and different variations of -- different forms of menthol have been found to have different effects; but I think there is only one kind of menthol or one class of menthol that is found in tobacco products.

DR. HENNINGFIELD: That's helpful.

And again, I will be asking all of the speakers to consider this, because it seems like a

very simple task, you know, consider menthol; but one of the things that we will have to figure out, if not in these couple of days, through the report development and so forth is, how is menthol defined? What do we mean by menthol? And is it a category?

I have a follow-up question --

DR. SAMET: Excuse me, Jack. Let me ask, Dan, if you can speak directly to this and clarify it, that might be helpful.

DR. HECK: Yes, I might be able to help some, Jack.

Brazilian menthol, natural menthol from mint plants -- well, we use to call it Brazilian menthol. It is sourced in other locations now. There are the natural product of commerce expected from mainly the corn mint plant, which is the cousin -- botanical cousin of peppermint. It does have other fractions -- you know, mint-like fractions. It is more complex than a single "P."

The current synthetic -- this is "L" menthol, the naturally occurring form. Currently, you can get synthetic L menthol, you know, very,

very fewer. And in practical use in cigarette industry both synthetic L menthol, and the natural menthol from the plant that has some other minty-like fractions.

The menthol, the isomer generally has kind of a musty taste, and it is mainly used in topical things like shaving cream, because it is not as useful for flavor purposes; and it is not as -- actually, with the TRPMA receptor either.

DR. HENNINGFIELD: This is going to be important because to the extent to which we talk about the effects of menthol, to the extent to which we try to figure out differences among studies, one of the questions is, what type was used? And to the extent to which we consider what, if anything, should be done about menthol, we would have to know what we're talking about.

My related question, though -- and again, this will come to other speakers, as well as Dr. Lawrence here on the hot spot right now -- so thank you for putting up with this. You showed a number of lines of information on both the effects

of menthol. And Dr. Heck mentioned that -- that in lower yield cigarettes -- and I'm paraphrasing -- that you have to increase menthol to get the effect.

Based on what you have seen, what is the effect? What effects of menthol on sensation, perception, physiology, behavior are we most confident of?

What is it that the -- for the smoker -- I mean, it seems obvious they can tell when they have got a menthol cigarette. I want to know what the data are. What the --

DR. SAMET: Let me help you out, Deirdre. If you can add anything to your presentation do so. Otherwise, I think Jack is asking the kinds of questions we are going to be delving into more deeply in our work as we write the report.

DR. LAWRENCE: Right. Well, confidently, which is the question that you asked me; I mean, certainly the cooling effects and the temperature changing effects have been well documented in both human subjects, as well as animal studies. So that we feel confident about. What does that mean?

That's a different question.

As well as the anesthetic properties or the analgesic properties, those have been well documented. Again, what does that mean?

So you are right, these are good questions in terms of we have seen well-documented properties; but how does that relate to topography? There are a lot of unanswered questions.

DR. SAMET: Okay. Dr. Clark.

DR. CLARK: Yes. Thank you. I have two questions. One for Dr. Caraballo.

You cite data from NSDUH. NSDUH is a household survey. There are a large number of people of color in institutions, principally jails and prisons. Do we know much about cigarette consumption in jails and prisons, or institutionalized populations?

DR. CARABALLO: There are not many studies, and I -- to tell you the truth, I did not look into that. To see the few studies that are out there if they look into what type of cigarettes they smoke. So the answer is, I don't know. I don't

know the answer.

DR. CLARK: The other question, if you get an opportunity to explore that, you want to look at the characteristics of cigarette consumption in an institutionalized setting, because it's a high stress environment, and we assume it might be --

DR. CARABALLO: The use is very high.

DR. CLARK: Yes; right. Thanks.

For Dr. Lawrence, even though the ends of the studies that you cited were small, did they report any ethnicity or race in those ends?

DR. LAWRENCE: Yes, they did report race, Black and White. So -- actually, I can go through them quickly if you would like.

DR. SAMET: Probably take too long to do that; but if you can just note that there are some studies.

DR. LAWRENCE: Okay. So yes, there were both Black and White subjects; but, again, reporting out the difference by race and by menthol status was not done.

DR. CLARK: Thank you.

DR. SAMET: Okay. Patricia.

DR. NEZ HENDERSON: Dr. Caraballo, one of the statistics that really stood out for me is the rate of menthol use among American Indians and Alaskan native. We are usually -- you know, when we look across that data set among smokers, American Indians are usually the highest. Do you have any idea in terms of your data set for both the youth and among the American Indian, Alaskan native adults why the rates are so low?

DR. CARABALLO: Well, when we are talking about prevalence of cigarette smoking, obviously, it's high, as was mentioned. In terms of why they are not smoking menthol cigarettes; why they are smoking nonmenthol cigarettes; I don't know. I know that there are tribe differences. Some tribes, you know, smoke more than others. I don't know if there is intertribal differences in menthol cigarettes use. So that would be one of those things that we would like -- you know, have to look into.

Unfortunately, again, as you probably know, these national data sets combine -- they just

ask, are you American Indian or Alaskan native? They even aggregate Alaska natives, which their cigarette smoking and smokeless tobacco use is very different to American Indians. So that's the problem. They aggregate everybody. So it's very difficult or impossible to piece out what's going on.

DR. SAMET: Let's see. Karen.

MS. DeLEEUW: Dr. Lawrence, one of the things that struck me about your presentation was the data that 60 percent of menthol smokers would pay more money for a menthol cigarette, than for a nonmenthol cigarette. That would potentially lead to a hypothesis that they may, in fact, be less price sensitive than nonmenthol smokers. Do you have any additional information about either race/ethnicity in terms of that sample of menthol smokers, would be the first question? And two, was there any additional information about pay more money and what that meant?

DR. LAWRENCE: Yes, this study was a two-page study. It was actually a letter to the

editor, and it didn't have a lot of details in it. It did have both Black and White smokers, and -- I missed your question. One more time, sorry.

MS. DeLEEUW: Were there any specifics about what the definition of what pay more money meant?

DR. LAWRENCE: No. Right. They just asked -- it's a very qualitative study.

DR. SAMET: Neal.

DR. BENOWITZ: Couple questions for Dr. Lawrence, and maybe Dr. Caraballo.

When you look at puffing behavior, two of the aspects that are really important determinants. One is ventilation and draw resistance; and the second may be nicotine content. So I think to make any sense out of the data one needs to look at the interaction between menthol and ventilation, draw resistance in context. Are such data available anywhere?

DR. LAWRENCE: That's a good question. The way that the studies were done, it was suppose to control for the resistance with the flow meter.

So it was suppose to control for the resistance that you described. But in terms of more detailed information about various nicotine yields for menthol versus nonmenthol, those studies were not done.

DR. BENOWITZ: Okay. And the second question, you talked about a Krakowski study that suggested that heavy smokers, more than 20 cigarettes per day, preferred higher levels of menthol; and moderate smokers preferred moderate concentrations. But this seems to go against what we know, which is African Americans, on average, smoke fewer cigarettes than Whites; but they smoke more menthol cigarettes. I wonder if you or Ralph actually have data looking at the relationship between menthol and cigarette consumption by race.

DR. CARABALLO: Yes. The study that I was referring to that we were looking from the NHANES to cotinine levels varied by menthol use versus nonmenthol use. This is based on some reports, but there was no difference between those of the same race. Those who smoke menthol versus nonmenthol

cigarettes they were almost exactly the same.

So African Americans that reported of menthol cigarettes self-reported almost the same amount of African American of nonmenthol cigarettes; similar for Whites, and similar for Mexican Americans. So at least in that one study we found no difference between the two.

DR. SAMET: Dorothy.

DR. HATSUKAMI: Dr. Lawrence, in your description of the cross-over studies, were those subjects nonmenthol smokers, menthol smokers, or a combination?

DR. LAWRENCE: So the groups contain both menthol and nonmenthol smokers. So we will put them together in one group. So that group was asked to smoke menthol cigarettes for a session; and that same group was asked to smoke nonmenthol cigarettes. So you had menthol smokers smoking menthol and nonmenthol cigarettes; and the other way around.

DR. HATSUKAMI: Okay. Thank you.

Also, what was the relationship between the smoking topography and biomarkers of the

exposure? Did they look at that as well?

DR. LAWRENCE: Yes; and Dr. Hoffman will talk about that later. For some of the studies, carboxyhemoglobin, I believe, was measured, as well as carbon monoxide in terms of short-term biomarkers of exposure. Dr. Hoffman will talk about that later on today.

DR. HATSUKAMI: Then, Dr. Caraballo -- Ralph, in the studies that you had done, can you measure trends in terms of number of cigarettes smoked among the menthol smokers over time?

DR. CARABALLO: I believe that NSDUH collects cigarettes per day. I'm not completely sure. I would have to look into that; but if they do, then the answer is yes.

DR. SAMET: Okay. Greg.

DR. CONNOLLY: Dr. Lawrence, in your slide 13 you state the sensory properties, and they include analgesic effects, and local anesthetic effects. The references seem to be to menthol generally -- you don't have to do that. But my question is, in the levels that we see in smoke, do

we see analgesic effects? And do we -- and do we see local anesthetic effects? Do we know that?

DR. LAWRENCE: Oh, I see what you are saying. As opposed to dermally applying?

DR. CONNOLLY: Yes, because the three studies you reference do not allow cigarette smoking.

DR. LAWRENCE: That's right. Yeah, we don't know.

DR. CONNOLLY: Okay. And would we assume there would a dose-response relationship between an analgesic effect and a local anesthetic effect based upon the dermal studies?

DR. LAWRENCE: Right.

DR. CONNOLLY: So I think those were important questions that should be answered or addressed.

DR. LAWRENCE: But it's an assumption.

DR. CONNOLLY: Well, the published literature that you referenced for dermal studies show that menthol has an analgesic effect.

DR. LAWRENCE: Yes.

DR. CONNOLLY: And has a local anesthetic effect.

DR. LAWRENCE: Right.

DR. CONNOLLY: Now, it would be my understanding that within the oral cavity there are tactile receptors that are the same nature of dermal receptors; and potentially they are the same effects, but we don't know the levels.

DR. LAWRENCE: Right.

DR. CONNOLLY: Thank you.

DR. SAMET: Melanie.

DR. WAKEFIELD: Another question for Ralph.

Given that we see there is some gradual drift among all smokers towards menthol over time in your data, are there some kind of gross effects of the population level that might account for that in terms of tobacco marketing, things like price discounting of menthols, marketing of certain mentholated brands that has become more vigorous over time? What would you say on those?

DR. CARABALLO: I didn't look into that.

I know that there is going to be a marketing presentation. So hopefully, they have looked into that.

DR. SAMET: Okay. I just have a few questions left, believe it or not. So Ralph, question to you.

In terms of the interpretation of the survey data from the question that you gave, I cannot quite tell how people who might smoke both menthol and nonmenthol brands would be counted.

DR. CARABALLO: I will have to look at the question exactly. I will say in the past 30 days, you know; I don't know if they use most frequently; I don't think so. I will have to look at it again, you know, the question from NSDUH.

That's a good question. I don't know because of what I mentioned. I think that this will be more of a problem with adolescents that may have smoked both. We know that adults, the vast majority of them, they're established smokers and they have a brand preference, more settled, you know.

So I think that even though there may be

some misclassification of smoking both of them, that will be, I assume, minimal among adults. It may be much more of a problem among kids. Now, how to compute that, how to characterize it -- what is the magnitude of that, you know, we don't have that information.

DR. SAMET: I think it would be useful if you could clarify it. As I understand, again, the question that was asked we would have to interpret the responses as any contact with menthol -- the use of menthol cigarettes in the last 30 days without providing information on the proportion of smoking that was menthol.

DR. CARABALLO: Right.

DR. SAMET: If you can help us, perhaps, with follow-up on how to interpret those.

DR. CARABALLO: Sure. I think we can look into -- just to get a sense. We may not get a direct answer, but to get a sense looking at daily smokers among -- let's say among youth, daily smokers versus occasional smokers, see if there is any differences there. That may tell of some sense,

you know between the two groups.

DR. SAMET: Thank you. Couple of quick questions. Any -- did you find any papers related to biomarkers of menthol itself? Has that actually -- has anyone ever looked at that, or is any such data available?

DR. LAWRENCE: I didn't see that. Did you, Dr. Heck?

DR. HECK: I think Dr. Benowitz in his 2004 study was -- urinary menthol, we have had trouble finding that same figure, which would be plasma menthol or biomarker menthol excretion from the smoking source only. It is surprisingly relatively rarely done.

DR. SAMET: So this may be something we want to return to after the biomarker presentation.

And then also in your studies -- again, recognizing your professional background -- but did you find anything on what happened to the external receptors with prolonged exposure to menthol?

DR. LAWRENCE: The only thing that I saw was there was this increased tolerance that we

talked about. So with menthol having an initial irritating property; but then after applying menthol over and over again, there was a tolerance developed. That's the only thing that was described.

DR. SAMET: And receptor numbers are down -- regulations on receptors?

DR. LAWRENCE: That, I don't know.

DR. SAMET: Okay. Okay. Other questions before we break for lunch?

Okay. Corinne.

DR. HUSTEN: I just wanted to clarify one thing about the studies that we looked at, because I think on -- some of the questions were related to this. We primarily were searching for studies on cigarettes. There is vast literature on menthol itself as a compound. We didn't try to search that whole literature, because we were unclear, for example, if it's a property seen when it's applied to the skin, and how relevant that was, or even oral, since this is cigarettes and smoke.

We did do a little bit were we needed to

just sort of explain what menthol was, and a little bit about its properties; but for the most part, the analysis was restricted to studies related to menthol cigarettes.

DR. SAMET: Okay. Thank you. Then, we are on schedule for lunch. We will reconvene at 1:00. Again, let me remind the Committee members, no discussion on the committee topic during lunch, amongst ourselves, or perhaps any members of the audience. So back at 1:00. Thank you.

(Whereupon, a lunch recess was taken and the proceedings subsequently reconvened.)

DR. SAMET: And what we're going to -- what we're going to do is hear from Dr. Rising, consumer perceptions of menthol cigarettes. Then we will have clarifying questions. And then we will do the three, initiation, dependence and cessation. That will be Drs. Rising and Hoffman; and then clarifying questions. Then the last will be the potential health effects of menthol, and clarifying questions. I think it's a somewhat logical grouping of these. So Joshua.

DR. RISING: Okay. Thank you very much. It's an honor to be before the Committee and the audience here today. I will be talking next on the perceptions and marketing of menthol cigarettes.

So the topics of interest that I will be discussing during this particular presentation. First, how do adults and youth smokers perceive menthol cigarettes? We will also look to see what data, if any, there is on racial and ethnic subgroups and on women. We will be looking at the potential role of marketing in the formation and continuation of these perceptions. Then, finally, we will look to see what's in the published literature, if anything, on the tobacco industry knowledge of these perceptions.

So before we get into some of the meat of the talk, just some background introduction as to why we're spending time talking about marketing and perceptions during our session here today. So the first of that understanding perceptions is important to understanding utilization.

Certainly, if we're trying to understand

human behavior here, it is a very complex topic. Then, it's important, as we try to understand that human behavior, to understand the perceptions that can be a factor in the decision making that goes into these complex processes.

An important caveat is that perceptions can certainly result from many different drivers. So to give one example, and we will see some evidence later today that menthol cigarettes are often perceived as soothing. Now, there can be many different reasons as to why that's the case.

Certainly, one could be a marketing reason. Kind of the advertising campaigns lead people to perceive them as soothing. Another could be a biologic function, in that they produce a physiologic reaction that is perceived as soothing to the individuals who use those products.

Another driver could be family and friends. Other people whose use the product say that they are soothing. So it gets passed on in a word-of-mouth sort of way. Many different drivers go into the formation of perceptions.

Then one other caveat is that the research that's been done that we will talk about today on perception on menthol cigarettes often uses a comparison. So when they ask people how do you perceive menthol cigarettes, it's often in comparison to something else. So nonmentholated cigarettes, or a couple other examples that we will get into, there is often a comparison that is used in the research on perception.

A couple of limitations before we get into this as well. You know, clearly like the other topics we have seen, this is a challenging topic for research; and trying to understand any causal linkages is going to be very difficult.

There is not an extensive amount of literature on this topic like with some of the other topics with menthol. So, again, it makes it difficult to draw conclusions.

Furthermore, the literature that we're going to see is kind of also subject to further limitations. Some of the literature we will be talking about today is conducted with focus groups,

has small sample sizes. They have other reasons why general likability of this particular literature could be difficult. The final limitation, again, is we are trying to understand human behavior, which we certainly know is multi-factorial.

So, again, you kind of have seen this slide before. After doing the initial literature review from NCI and the recent additions, we identified a total of 26 articles that were specifically relevant to this particular presentation on perceptions and marketing.

So the first thing that we looked for data on is what were the perceptions of youth? What do youth -- kind of defined in general as individual under the age of 18 -- what do they think or perceive of menthol cigarettes? And in the literature review that we had done, we weren't able to identify any studies that particularly answered that research question.

Then moving on to adult perceptions. What does literature say about the perceptions of adults of menthol cigarettes?

So looking at the data, there were three studies that looked at this question. The first was a study of 213 menthol cigarette smokers at a cessation clinic, and asked them why do you smoke menthol cigarettes?

Kind of going down the list of the most frequent perceptions that were involved in the answers they gave, the first was menthol cigarettes taste better. 83 percent of blacks, 74 percent of Whites gave that response.

Next was, in response to that, menthol cigarettes were more soothing to my throat. Again, this is more soothing in contrast to nonmenthol cigarettes. This was about half of both Blacks and Whites.

Next was, I can inhale menthol cigarettes more easily. There was a little bit of racial difference in this answer, 48 percent of blacks and 21 percent of Whites.

Next, I can inhale menthol cigarettes more deeply. About a third of Blacks and 10 percent of Whites.

I have always smoked menthol cigarettes. Almost two-thirds of Blacks, and 39 percent of Whites gave that answer.

Menthol cigarettes are better for you. Seven percent of Blacks, and five percent of Whites gave that answer.

Then, a final one related to advertising. Most of the advertising I see is for menthol cigarettes. Ten percent of Blacks, and three percent of Whites gave that answer as to why they smoke menthol cigarettes. Again, this is why you smoke menthol in comparison to non-mentholated cigarettes.

The second study was a focus group of Black smokers who were age 45 to 64; and they were asked a variety of questions related to cigarette smoking in general. Then, they were also asked to specifically give their perceptions of menthol cigarettes and of nonmenthol cigarettes.

The first -- so when asked about menthol cigarettes, they described them as refreshing, soothing, and smooth. Nonmenthol cigarettes were

described as strong and harsh.

They were asked to compare the safety of different types of cigarettes. They were asked about light cigarettes. They were asked about menthol cigarettes, and then traditional nonmenthol cigarettes. And, again, light was a term that was used by the authors of the study.

And when asked to compare these, this focus group felt that light cigarettes were the safest of the three options; and that the traditional nonmenthol were the most dangerous, and that the menthol cigarettes were in the middle, in between those two.

Then, this focus group also had a sense that menthol ads were more prevalent in black publications and black neighborhoods.

The third study also involved focus groups. These focus groups that were of younger individuals, 18 to 22 years old. The focus groups were broken up by racial or ethnic groups. Some of the focus groups had White individuals, some had Hispanic individuals, and some had Black individuals

in the focus groups. Total of 16 groups were conducted; and, as I said, they were segmented by race and ethnicity.

So trying to boil down the results from this particular study. So first non-Hispanic White individuals in the focus groups in general felt that menthols were less safe than were light cigarettes -- again, light term used by the authors. But when asked to compare menthol to nonlight, nonmenthol cigarettes, they did not have consistent safety perception.

Again, this was a study that was trying to compile a lot of different opinions from the individuals in the group, so there was a range of opinions that they had.

Next, looking at black individuals in the focus groups. They felt that menthols were less safe or maybe equivalent to light cigarettes; but didn't have consistent safety perceptions when comparing menthol to nonlight, nonmenthol. And black individuals compared to other ethnicities were most likely to select the same risk option when

comparing different type of cigarettes.

Finally, looking at Hispanic individuals in the focus group. Hispanic individuals, in general, didn't have consistent safety perceptions when comparing menthol to light or nonlight, nonmenthol cigarettes. Those were the three studies that we were able to identify in the literature that looked at adult perceptions of menthol cigarettes.

Now, segue a little bit to some of the marketing history of menthol cigarettes and see what information, if any, that gives us to understand some of the perceptions.

The literature has, in general, identified four messages or themes that have appeared over the years that have been used to advertise menthol cigarettes. The first three of these appear chronologically, and the fourth was more of a cross cutting theme from a time perspective.

So the first real theme that was out there was a healthy, medicinal one. We will get into a little bit more detail on these. The second chronologic theme was a fresh, refreshing, cool, and

crisp. The third was a lifestyle theme that focused on youthfulness, silliness and fun. And the final one was an ethnic awareness theme.

So the healthier medicinal theme. Early marketing messages suggested using menthol cigarettes when individuals had irritated throats or had a cold. There was frequent use of the word "soothing" in these particular advertisements. This ended in the early 1950's.

The next one to come along after that was the fresh, refreshing, cool and crisp theme. And again, these were ads that would frequently appear themselves in the -- the words would appear in ads for menthol cigarettes. Often these ads had natural themes that would accompany the text. People on tubes, going down the river, hiking through forests; the kind of very outdoorsy theme. '60 and '70 were the primary time where this theme appeared.

The next theme of the literature identified was this lifestyle one; and said that this one really predominated from the 1970's onward; and kind of a Newport theme. "Alive with pleasure"

is given as one example of this particular theme.

The final theme that the literature identified for advertising menthol cigarettes was an ethnic awareness theme. And the literature describes this as really arising as a post World War II marketing effort. It was targeted at minority populations largely. It was often aligned with sophistication or cool themes that appeared in the advertisements and the literature. There was extensive pop culture usage that accompanied these particular ads, and there was some frequent use of marketing firms that focused on specific racial and ethnic groups as a part of this particular theme.

We will now take a look to see what data there is on marketing, and whether there was differential marketing of menthol cigarettes, or differential response as we look to see what the published literature had to say about the impact and data on marketing.

As to the first, looked at promotional offerings, which are the largest component of advertising from tobacco companies in general. There

was one study we identified that found that menthol cigarette smokers were more likely to use promotional offers than were nonmenthol cigarette smokers. This study found that almost 60 percent of menthol cigarette smokers used promotional offers. I think this particular study said everytime you see them versus 49 percent of Camel smokers, and 34 percent of Marlboro smokers.

In this particular study the confidence interval for the menthol and Camel groups did overlap; but the Marlboro one is the same for the menthol cigarette group. It didn't aggregate menthol and nonmenthol cigarettes and compare those two particular groups.

One important caveat with this study in looking at this analysis, it did not control for age, or income, or ethnicity; which other studies have found to be important factors in the use of promotional offerings.

I should have said at very beginning what do we mean by promotional offerings. In general, they are things that are thought of, for example, as

dollar off discounts or multi-pack discounts. Some different ways that can effect the price of the cigarettes. This particular study was -- surveyed about 4,500 individuals.

Next, we will look at what data there is on marketing to Black individuals. There were three studies that we identified from different time periods that evaluated cigarette ads that appeared in print media. In general, all these studies found that cigarette ads appearing in publications that targeted Blacks were more likely to promote menthol cigarettes. Kind of as one examples, one of the studies -- this was the Balbach study -- and apologies if I mispronounce any of the authors' names during this presentation -- but that study found that "Ebony" was approximately 9.8 times more likely than "People" to have an ad for menthol cigarettes.

Looking at other forms of advertising. We found one study that looked at billboard advertising. And the study found that in one urban location Black neighborhoods were approximately twice as likely as White neighborhoods to have ads for menthol

cigarettes. That was the Altman study.

Another one looked at point-of-sale advertising. This was the Law study. And this found that about one-third of the ads in Black neighbors, the point-of-sale ads in the stores, were for menthol cigarettes versus approximately 10 percent for White neighbors. This was also statistically significant.

And then, finally, one study looked at promotional offerings. The same study that we looked at earlier did then do a separate analysis looking just at Black individuals and their use of promotional offerings. And it found that two-thirds of Black smokers who smoked menthols used promotional offerings, whereas only about a third of those who did not smoke menthols use promotional offerings.

One other study on the impact or data on advertising to Black individuals. One study that was a retrospective recall of exposure to tobacco advertising by low income black smokers in one urban setting. About 70 percent of this group smoked menthol. These were adults who were then asked to recall their exposure to ads as children.

It is found that currently both men and women were more likely to use menthol cigarettes if they were exposed to menthol ads in the current time period. And then the study found that women were more likely to smoke menthol cigarettes if they reported exposure to menthol ads as children. Though, again, there certainly needs to be some caveat with the difficulty of retrospective studies such as this.

Now, turning our attention on the data on marketing to Hispanic individuals. Some of the same studies that we saw earlier also reported results for Hispanic individuals. So the first one, the Landrine study, found that the Spanish version of "People" was about two and a half times more likely than the English version to have a menthol ad.

You saw earlier the Altman study found that Hispanic neighborhoods had more billboards for menthol cigarettes than did White ones. It was 17 percent versus 11 percent; though, statistical significance was not reported with this.

Then the final one, the Law study, on

point-of-sale study, also found that there were higher rates of advertising for menthol cigarettes in Hispanic neighborhoods than in White ones.

Moving to data on marketing to women. In general, this was a topic in the literature that we did not find very much research on at all. There were certainly some comments in some of the papers that noted that the ads for menthol cigarettes were generally designed to appeal to women, but there weren't specific studies that we identified that looked at this in more detail.

We then looked to see what data there was on the marketing of menthol cigarettes to youth and young adults. Just as a brief point of background, it's been well established in the literature that youth are particularly susceptible to advertising; and that both exposure to advertising and receptivity to advertising are important contributing factors in the initiation of smoking.

One study that we identified held five focus groups with youth who are age 12 to 13 years old. These focus groups had few current smokers.

This discussion was not focused on menthol cigarettes specifically. One individual did start talking about some of the ads that he had seen for menthol cigarettes. You can read the quotation here that gives his impression for the ad that he remembers.

Another study explored the prevalence of menthol marketing to youth. This particular study was -- explored the prevalence of advertising in retail stories in Hawaii. The study found that a menthol brand was the most widely advertised in indoor and outdoor settings. The study also noted that this was the same brand that was most widely smoked by youth in Hawaii. The study does go on to state the difficulty of drawing any causal conclusions from this particular association, but did note that the association existed.

One other study we identified that was relevant to the marketing of the menthol cigarettes to youth and young adults; the Mazis study asked participants to judge the ages of models appearing in cigarette ads. So it divided the cigarette ads into two categories. There were menthol ads, and there

were ads for nonmenthol cigarettes. So it then asked the participants in the study to estimate how much they thought the models -- how old the models were who were appearing in the ads.

This study found that the perceived age of models in ads for nonmenthol cigarettes was about 32 years of age. But that the perceived age of models in ads for menthol cigarettes was about 25 and a half or 26 years of age.

We will now look to see what information there was in the published literature on the publicly available tobacco industry documents and consumer perceptions.

So from a published review of these publicly available industry documents, one document stated about adult perceptions. There are indications that menthols tend to be considered generally better for one's health. That impression refers not only to the health of the respiratory tract, but the whole organism. The majority view is that menthols are less strong than regular cigarettes; and that a cigarette which is less strong

is better for a person's health. That's from a 1968 document.

Again, kind of looking to see what information there was on perceptions of adults from tobacco industry documents. Another published review found information in industry documents that Black smokers were more likely to believe the following about menthol cigarettes. That they were better if you smoke a lot. That menthol cigarettes were lower in tar and nicotine. They were less likely to make you cough. Menthol cigarettes were better when you have a cold, and they were less irritating to the throat. And this was from a 1979 document.

And continuing our exploration of information on adult perceptions, from a published review of publicly available industry documents, one showed that there was some industry awareness of varying desires of menthol smokers. That not all menthol smokers were looking for the same experience from their cigarettes.

All three major brands, Salem, Kool, and Newport built their franchise with younger adult

smokers using a low menthol product strategy. However, as smokers acclimate to menthol, their demand for menthol increases over time. Responsive brands whose strategy is to maximize franchise value, invariably increase menthol levels over time. That was a quote from a document in 1986.

We look to see if there is any information on perceptions of younger smokers in the documents; and from a published review of publicly available industry document, one document showed knowledge of the appeal of lower menthol cigarettes, specifically to younger smokers. The want for less menthol does, indeed, skew younger adults. That was from 1978.

A little more information on adult perceptions -- sorry, this should be younger adult perceptions. So from post review of publicly available industry documents, one document showed interest in the smoking patterns of Black youth, and in strategies to enhance the position of menthols in this population.

The quote is, in order to gain a foothold in this young Black menthol market, we have to offer

them a cigarette that they want, and what they want is a high delivery cigarette. That's from 1982.

Looking to see what information there was in recent changes in menthol products that would be relevant for this talk on marketing and consumer perceptions. The literature documented from industry documents, documents a number of changes in menthol products over the past decade. So the literature noted that there had been an introduction of new menthol brands that had lower menthol levels than the other brands on the market. It gave Salem Black and Marlboro Mild as examples of that.

I noted that there were some brands that were already in existence that reduced the amount of menthol that was in the cigarette, and it cited Newport and Kool as examples of that. Noted that other brands had increased their menthol levels; it gave Marlboro Menthol as an example of that particular change.

Then the quotation from the review of the industry documents concluded, we found evidence that the tobacco industry introduced new menthol brands to

gain market share, particularly, among adolescents and young adults.

So returning to the topics of interest that we started this presentation with. So the first -- and again, the appropriate caveats of there not being an abundance of this literature, and the appropriate caveats with the literature that does exist, the verse is that, research studies and reviews of the publicly available industry documents suggest that menthol cigarettes may be perceived to be safer choices.

We saw that marketing campaigns and perceptions stress similar themes, and that the campaigns have focused on Black smokers. To give you an example of what I mean by stress similar themes, returning to the notion that we started with, a perception of soothing. You know, we saw that this was a perception that individuals have, and we also saw that that was part of a marketing campaign that had existed at one point and time.

And then, finally, we also see that tobacco industry documents differentiate the preferences of

younger smokers with those of experienced smokers. And we saw that there have been a number of changes in cigarette menthol content over the past decade. Clarifying questions?

DR. SAMET: Greg.

DR. LAUTERBACH: That was very, very nice.

What do we know about the consumer group's focus on retail products, and how reproducible they are from session to session, or different parts of the country? Any studies been done on that, not just on cigarettes, but other consumer goods?

DR. RISING: So asking about the methodology of focus groups generally, and kind of what we know about how reproducible the information is?

DR. LAUTERBACH: Right.

DR. RISING: So it's a good question. Certainly, was not included as part of a focus of this topic here. So I would kind of be hazarding a guess if I talked about it. Certainly, there are ways to conduct focus groups well to gain some useful information, and there are ways to do them

less well; but beyond that, I will hold off.

DR. SAMET: Okay. Ursula.

DR. BAUER: I asked in the earlier session when we were looking at the prevalence data that seemed to show an up tick in use of menthol cigarettes among adolescent smokers, in particular, whether there had been an influx of sort of new menthol options on the market. And you seem to be suggesting from your review that, indeed, there were not only new menthol products introduced in the same time period that coincides with that up tick; but that, specifically, there were lower menthol products; sort of a more introductory product.

DR. RISING: Certainly, there were some new products that were introduced. As to exactly what the numbers were, you know, I don't want -- certainly, from the review of the literature I can't say there were ten more products in 2008 than there were in 2000. Certainly, there were some new ones introduced, and they were introduced at a lower menthol level than some of the existing ones. Beyond that, there wasn't information in the

literature that kind of aggregated the numbers or the amount of sales or anything along those lines.

DR. SAMET: Greg.

DR. CONNOLLY: Thank you. Very good presentation.

I was intrigued by -- you presented data on cognitive beliefs to messages of safety. They seemed fairly low. Am I correct in saying that? That people when asked directly, do you believe this is a safer product, the score was relatively low?

DR. RISING: Low meaning they weren't able to make a decision, or --

DR. CONNOLLY: Well, they seemed to be on the -- responding -- a cognitive belief in safety seemed to be not as high as when you asked questions of the perception of soothing, smoothness. Am I correct in saying that? That people were perceiving the effect of menthol to be higher than the cognitive belief and safety.

DR. RISING: Yes. So you know, given kind of the number of studies, I think it's difficult to make kind of comparisons between those things. You

know, kind of the one study, you know, that we talked about that had the soothing and smooth, you know, was kind of one study of 200 smokers; and then kind of the other safety ones were, you know, some focus groups. So trying to compare those relative to each other is --

DR. CONNOLLY: Well, I just saw -- I think more research in that area would be very helpful for the Committee, because their seem to be, just even in those few studies, differences.

The second question is, did you look at commercial data sets to look at specific brand sales -- let's say, for Newport, Kool -- over periods of time? One brand increase in market share versus -- over another brand from a commercial data source.

DR. RISING: So the only data sources that we used for this were kind of the ones that were identified in the original NCI literature, and then the supplemental one afterwards. So if there was data from else were, we didn't include it.

DR. CONNOLLY: Just saying for the

Committee, commercial data sources. Did you look at commercial data sources on advertising to see if there was increase in expenditures for menthol advertising over the past ten years versus nonmenthol advertising.

DR. RISING: Yes, one of the reviews discussed magazine advertising a little bit, but otherwise there wasn't any kind of other inclusion on data on the amount of advertising in the literature.

DR. CONNOLLY: I think that that would be important if it is available.

Did you look at data -- when you referenced -- when you represent a promotion, do that include the variety of promotions, or was it more focused on price discounting, did you know from the research?

DR. RISING: So the one thing on promotion offerings, I would have to look back at how they phrased their questions; and how they defined what a promotional offering was. I would need to look at that again.

DR. CONNOLLY: Okay. Well, again, for the Committee, I think it would be helpful to look at the issue of price discounting in variations were price discounting may occur; geographically, ethnically, by brand. But I think the presentation was a very, very nice presentation. Thank you.

DR. RISING: Thank you.

DR. SAMET: Actually, I think, Josh, just to clarify, your review was entirely based on the NCI bibliography, is that correct; or did you have other sources?

DR. RISING: Right. So it's that bibliography; and then, you know, in January of this year we then did another search with the same terms to identify subsequently published studies.

DR. SAMET: These are all published studies, and not any other primary data sources, just to be clear. I think that gets to Greg's question.

John, do you have a clarification?

DR. LAUTERBACH: Any of these public references that you used cover store brands or

nonadvertised brands?

DR. RISING: I'm sorry, so the studies?

DR. LAUTERBACH: Yes, the studies.

DR. RISING: So did they -- I mean -- I guess I'm not quite sure what your question is.

DR. LAUTERBACH: For example, there is numerous brands of cigarettes today and some of them are heavily advertised, and some of them are store brands, some are very much generic brands, some are regional brands. Is there any information we have on those versus the major brands in terms of the marketing perception?

DR. RISING: So in terms of kind of people's general perceptions the study asked, you know, menthols compared to nonmenthol. So for more regional brands depends on whether they were considered as a menthol cigarette versus nonmenthol. Then, the more specific advertising, certainly the ads where you were comparing, you know, "People" to other magazines, those would be brands with national advertising. The studies that looked, for example, at the point-of-sale advertising, you know, in urban

areas could potentially include some of the regional or local brands.

DR. SAMET: Okay. Jack.

DR. HENNINGFIELD: I guess what was amazing to me is how little public information we seem to have on the many aspects of consumer perceptions that a marketer would need to do their marketing, to guide decision making on advertising. And I'm wondering about other potential data sources; and maybe mention this do -- is the Federal Trade Commission -- do they have data that you are able to tap into? Is that a potential data source that we should be thinking about tapping into?

DR. RISING: I think it is a potential source. I don't know the answer to that one way or the other. You know, certainly, we have been building strong relationships with Federal Trade Commission like with other federal agencies, so I'm sure that's something we could explore.

DR. HENNINGFIELD: And the kinds of things I am thinking of -- some of it go back to my favorite issue, dose, and how much is in there and

what drives changes over time. So you talked about changes over time, and I'm curious as to any data that you saw that -- any information that would have guided those changes, assuming they are not grounded.

DR. RISING: Changes in the marketing themes and messages?

DR. HENNINGFIELD: Well, not only the marketing themes, but changes in menthol dosing levels. The lower dose brands that came out in 2000, 2003. Any inkling as to why the dose brands happened?

DR. RISING: Certainly, there is, you know, nothing that -- no causal associations that kind of exist out there. You know, kind of the one review that discussed these, you know, had some opinions in the review as to what was causing some of the changes; and kind of the increase -- or introduction of some of the new brands; but no other studies that really looked at that question.

DR. HENNINGFIELD: Just a couple more of these kind of little probed. The interaction of

perception with exposure -- you discussed at the beginning where do perceptions come from? Are they created? Are they a result of exposure?

We know that from the light cigarettes experience people were told they were light, but then they would smoke the cigarette and they would feel light. So the exposure would reinforce the perception -- I'm over simplifying. Any evidence for that that you saw here, or -- in other words, how exposure interacts with what people are told?

DR. RISING: It's a good question. And you know, in general, I would say the literature was pretty silent on that issue. You know, difficult question to study in general, and we didn't find any evidence that really got at that, I don't think.

DR. HENNINGFIELD: And the last one, what were you looking for that you didn't find? You went into this probably with some of these same questions that I'm raising and more. And I guess what were you looking for that you didn't find? And can you think of any other place other than the tobacco industry itself were we might get the information?

DR. RISING: I mean, you know, I didn't go into this with a particular agenda or sort of things that I was necessarily looking for. We had kind of topic interest areas that we thought were interesting to explore. Then we saw kind of what the literature had to say about those particular topic areas.

So to the extent that we were able to answer some of those questions, then we found some of the information we were looking for. In the sense that we weren't able to answer some of those topics of interest in the beginning, then, we aren't able to find that.

DR. HENNINGFIELD: Thank you.

DR. SAMET: Neal, way down there.

DR. BENOWITZ: Couple questions. One is, when you were talking about different -- my sense you were talking about different levels of menthol within a brand. You say Newport may have high and low menthol. Is there a common perception among smokers that one variety of Newport is a stronger menthol brand than another? Is that something that

is common knowledge among smokers?

DR. RISING: So there wasn't any literature that we identified that specifically answered that. There were certainly discussion in some of the documents that kind of explored this particular issue, that this was the case. And there may have been a quote or two exploring that a little bit; but there certainly wasn't any kind of evidence in the literature of surveys of people saying, yes, I want a strong menthol brand. That's why I smoke this brand. So certainly, no; no strong evidence on that.

DR. BENOWITZ: Kind of a second question, you talked about differences in menthol content; but as you heard this morning the menthol delivery is determined also by ventilation. Are there any data anywhere about menthol delivery by standard smoking machine tests?

DR. RISING: Certainly nothing that I have seen.

DR. SAMET: Mark.

DR. CLANTON: I have a question for you

about perceptions that comes from the frontiers of pediatric and adolescent primary care.

Anecdotally, one of the few negative things that an adolescent smoker will admit is the perception that they have bad breath. In other words, they enjoy all the positive aspects of smoking, but they will admit that that's an issue; and will often take a hard candy or a lozenges that contains either a peppermint or a menthol.

Are there any surveys, or is there any data that tells us about the perception of adolescents who smoke mentholated cigarettes as it relates to some positive aspect to their breath?

DR. RISING: Again, didn't see anything on that. In doing this, I looked back over a number of different ads for menthol cigarettes over the decades. You know, there are definitely some ads here and there that would talk about the beneficial impact on breath specifically; but no more hard data than that.

DR. SAMET: Okay. Dorothy.

DR. HATSUKAMI: Related to what Jack was

saying, I think it would be encouraging to take a look to see if the lower dose menthol cigarettes was higher among the adolescent population. I think it would be fascinating if there is a data set that we can find to determine that.

One of the charges that we have is to take a look at what the impact of menthol cigarettes is among users, as well as nonusers. I am kind of curious in the studies that you had described in terms of adult perception of -- of menthol cigarettes. The third study that you talked about the focus to be, was that among nonusers or was that among users of cigarettes?

DR. RISING: The study that -- there were 16 focus groups or so that included many different adults.

DR. HATSUKAMI: Yes.

DR. RISING: So my recollection, that was all, among individuals who were using tobacco products of some variety, not necessarily cigarettes, but some tobacco products.

DR. HATSUKAMI: Okay. So there really

hasn't been any studies that you know of that have looked at nonusers and their perceptions of menthol cigarettes?

DR. RISING: No.

DR. HATSUKAMI: Okay.

DR. SAMET: Ursula.

DR. BAUER: I am having some difficulty interpreting some of the information that we have gotten here today, because we don't know the full community context, if you will. So, for example, you said smokers of menthol cigarettes are much more likely to use promotions than smokers of nonmenthol cigarettes. Is that because there are more promotional offers associated with menthol cigarettes? Or there are the same number of offers, but menthol smokers are just more likely to take advantage of them?

And how, as a Committee, do we kind of get some of that more community, contextual background so that we can assess some of the information that we are hearing? And I have a second question too.

DR. RISING: So yeah, good question.

So first -- so the study that had that finding -- with that finding was -- did not control for other factors that we know are also important in determining the use of promotional products. So I wouldn't necessarily say that -- you know, that we definitely know that menthol smokers are more likely to use promotional products.

There was also -- there was information on that study or in the published literature as to, are there more promotional offerings for menthol products? Are there fewer? Are they, you know, more focused in one geographic area, or in one population? That data wasn't out there.

DR. BAUER: The second question is that we hear that with smokeless products there is sort of a marketing transition that the new user is brought through, you know, sort of an introductory product that's much more mild, and then they progress up to the stronger and stronger product. Is there a similar perception with regard to menthol cigarettes, especially around some of these products that were introduced in 2000 and 2003, the low

menthol. So smokers would understand that they -- or they would have a desire for a stronger menthol cigarette, and they would sort of graduate up over time. Is anything in the industry documents that talks about that?

DR. RISING: So it is kind of a nice segue to the next talk on menthol and initiation of smoking. I think we will address some, likely not all, of your questions during that talk.

DR. SAMET: Okay. Other questions? Go ahead, sorry.

DR. NEZ HENDERSON: One striking finding is that overall there is more white smokers who use menthol cigarettes as shown from this morning's discussion -- or this morning's presentation. That there is more ads seen in Africa American communities and magazines. Does the literature or maybe the tobacco industry documents show anything -- why there is that discrepancy?

DR. RISING: It didn't address that. You know, certainly, we know that there are more Whites smokers; though, proportionally, you know, Blacks

use menthol much more than nonmenthol products. Nothing else as to why this particular advertising focus aside from that.

DR. SAMET: Okay. This is a question, but it's really not. Just in reference to your presentation, it would appear that most of the studies were somewhere in the last century. I mean, approximately what proportion of the data that you presented to us was collected, you know, in the last ten years?

DR. RISING: Yes. I have to go back and count, but certainly the majority.

DR. HENNINGFIELD: A follow-up on a couple of my earlier questions. Is there anything that would give you clues about what guided the changes in product that kept the marketing. So the marketing is based around a product. A product is presumably built for marketing to serve in these. So we have both brand extensions. We have the 2000, 2003 brands. Did you see anything that would -- assuming that's not a random process, making a new brand or a brand line, did you find anything that

gives us a clue as to where those ideas are coming from? What's guiding the brand development and brand line extensions?

DR. RISING: Yes, so there certainly wasn't kind of a lot in the literature on that. You know, there is the one study that had most of the quotations used here, and also outlined the change in menthol cigarettes. Kind of talked about, you know, the fact that there are two different groups of menthol smokers; you know, kind of those who like light, and those who kind of like more menthol. And the article posited that some of the changes could be related to that. Other than kind of that one article, there wasn't anything else in the literature that really explored that area.

DR. HENNINGFIELD: Thank you.

DR. SAMET: Okay. I think what we will do then, Josh, is move on to your next presentation, which would be the presentation entitled "Menthol Cigarettes and Smoking Initiation."

DR. RISING: Great. Now, we will turn our attention to the menthol cigarettes and the role, if

any, in the initiation of smoking.

The topics of interest for this talk include when does the initiation of smoking occur? When do people start smoking? Does this differ for menthol cigarettes, and does the timing of initiation vary by subgroups? Again, specifically looking at menthol cigarettes.

We will look at how prevalent is the use of menthol cigarettes among beginner smokers. So in this talk beginner smokers are those who have been smoking for less than a year, and that's how it appears in the literature on this subject. And does that vary by age, or by race/ethnicity?

We will also be looking at what the literature says about the relationship between the early use of menthol cigarettes and subsequent nicotine dependence. We will look at what data is out there about switching behaviors between menthol and nonmenthol cigarette products. Then we will look to see what, if anything, tobacco company documents say about the role of menthol and the initiation of smoking.

So the appropriate caveat for this one is that you can see that on this talk we're going to be drawing information and studies from eight different articles that are out there. So, again, kind of not a lot of data that is going to be present for this particular presentation.

So the first graph that kind of came up earlier about the initiation of smoking. So this graph, kind of from the 1990's, explores when individuals start smoking. So these are people who are aged 30 to 39, and who are asked questions about when they started their smoking behaviors. They are asked two questions: When was the age you first tried a cigarette? That's the blue line here.

Then what was the age where you began smoking daily?

For example, kind of -- can't really see the pointer -- so you can see -- so if you follow-up the line from age 18, you can see that at age 18 somewhere between -- somewhere around 90 percent of people who were smokers had begun their -- had tried their first cigarette; and about 70 percent had

begun smoking daily by age 18. Then when you get to age 24, over 90 percent of the individuals had begun smoking daily by that particular age.

So when we're exploring the topic of initiation and trying to understand initiation better, we're really most interested in individuals who are younger, really younger than 24, as that's when the vast majority of initiation of smoking occurs.

There is another study by Trinidad in 2004 that explored some of the same questions. When was the age of regular smoking onset? So this was a tobacco use supplement to the current population survey. This question was asked of individuals who were age 26 to 50; and it asked them when they began started smoking. Again, you can se that the vast majority of smoking onset occurs at age 21 or younger.

This particular slide also demonstrates a little bit of racial and ethnic variation as to when the age of initiation occurs. Again, this is for all cigarettes broadly, not specifically for menthol

cigarettes.

So according to this study, you know, you can see that Asian and Pacific Islanders begin smoking later than do some other racial and ethnic groups; and that African Americans also start smoking slightly later than do some other racial and ethnic groups.

So now look to see what the literature says about menthol cigarettes use by new youth smokers. Again, youth defined as under age 18.

So the first study from the National Youth and Tobacco Survey in 2002. This was a survey of 36,000 students. And asked of current smokers whether they smoking menthol cigarettes or nonmenthol cigarettes. Then broke these into new smokers -- so people who have been smoking less than a year; and experienced smokers -- those that have been smoking for more than a year.

When it looked at middle school students, it found that about 62 percent of new middle school smokers smoked menthol; and about 53 percent of experienced middle school smokers smoked menthols;

and they found this difference was statistically significant.

They also looked at high school students, and asked kind of the same question, and they found a slight difference that was not statistically significant. That was 46 percent of new high school smokers smoking menthols; and 42 percent of experienced high school smokers smoking menthols. Again, cross sectional study, so difficult to know whether this was a cohort effect, or whether this was individuals transitioning from menthol cigarettes to nonmenthol cigarettes.

We're now going to be looking at the National Survey on Drug Use and Health, the same data source that was used for the presentation earlier today. Again, this is asking -- this is looking at new smokers, the blue line, versus experienced smokers, that's the red line -- or the green line. Those are people who have been smoking for more than one year, and ask these groups, do you smoke menthols or do you smoke nonmenthol cigarettes?

And you can see that for most of the years of the survey 2004 to 2007, the new smokers were more likely to be smoking menthols than were experienced smokers. You can see there is a slight kind of change in that graph in 2008; and we're going to need some more data points to understand if that is a one year aberration, or if that is a reversal or change in the trend that had been going on.

We're now going to turn our attention from youth to menthol cigarettes use by new young adult smokers. Similarly, the data from the 2004, 2008 National Survey on Drug Use and Health found that new smokers, age 18 to 25 -- so the young adult group -- were more likely to prefer menthol cigarettes; 40 percent versus 36 percent. This particular publication did not mention whether or not that difference was statistically significant.

Moving on to the age of initiation, when people start smoking, and whether menthol cigarettes play a role in that. There were two studies that were identified in the literature that had data

relevant to this question.

So the first was the COMMIT trial, published in 1995; and this Trial asked retrospective questions as to when current smokers began smoking, and also collected data as to whether they smoked menthol or nonmenthol cigarettes at the time of the survey. The study didn't find any difference in age initiation between those who smoke menthol cigarettes and those who smoke nonmenthol cigarettes.

One other study, the CARDIA trial published by Pletcher in 2006. Again, this asked retrospective questions. There were about 1500 enrollees in this study, about age 25. And asked them to recall when they had started smoking. And again, divided these into current menthol smokers and current nonmenthol smokers. And this also found no difference in age and initiation between those who preferred menthol cigarettes and those who preferred nonmenthol cigarettes, again, at the time the study was conducted. So it did not ask, was your first cigarette a menthol cigarette or a

nonmenthol cigarette.

Moving on to early menthol cigarette use and subsequent nicotine dependence. What, if anything, is in the literature on this particular topic. There is one study that we identified in the literature in this area. So this was a longitudinal study of seventh graders that was conducted. It was a study of a total of 679 seventh graders, and followed them for 30 months. Of these 679 seventh graders, 237 of them reported that had inhaled a cigarette either before the study or during the course of the study.

Of the 237 -- this, again, shows some of the difficulty with data collection in this area -- about half of them could report if the first cigarette was a menthol cigarette or a nonmenthol cigarette.

They kind of assessed whether there had been a difference in reaction. How did that cigarette make you feel, you know, kind of right afterwards? Good effects, bad effects of that first cigarette. They didn't find have any difference in

reported reaction to the first cigarette between those who reported that it was a menthol, and those who reported that it was a nonmenthol.

Then kind of they used a nicotine dependence scale towards the end of the survey to try to assess how dependent any of the individuals were. They did not find that there was any difference between the group that reported their first cigarette was a menthol, and those who reported that their first cigarette was a nonmenthol. Again, very small study, and only about 100 and change individuals who could report whether it was a menthol or not.

Now, we're going to look to see what is in the literature on switching that individuals do between menthol and nonmenthol cigarettes. One study followed current adults smokers within the Kaiser Permanente system, for a mean of about four and a half years, between 1979 and 1986. This publication looked at approximately 1700 black smokers who were followed as part of this cohort. Found that about 14 percent during the study period

switched from a nonmenthol cigarette to a menthol cigarette. Then found that about three and a half percent went the other direction, were smoking menthols, but then switched and were smoking nonmenthol cigarettes.

Another study, in contrast, found that there was really no difference between these two. Again, this was the Pletcher study that we saw earlier. During the course of the follow up, which was about 15 years in duration, they found that 12 percent of the participants switched from menthols to nonmenthols; but pretty evenly balanced between the 11 percent who switched from nonmenthol cigarettes to menthol cigarettes during the course of the 15 year study.

So looking to see what was published from publicly available tobacco industry documents about menthol and initiation. As we look -- and there is one published review that explored this issue; and this review had one quotation from tobacco industry documents as to how menthol cigarettes could help new smokers overcome negative reactions. First time

smoker reaction is generally negative. Initial negatives can be alleviated with a low level of menthol. That's from a 1986 document.

Returning to the topics of interest from the beginning of the talk. So we see and we know that the initiation of established smoking behaviors occurs almost exclusive before the age of 25. We saw that menthol cigarettes are more widely used by beginning youth smokers than by established youth smokers. Though, again, kind of a change in the trends from that one data source in 2008 needs some more exploration.

There is really less data on young adult and adult beginning smokers and any preference of menthol cigarettes among that age group. There is limited data, but the data that is there do not suggest that menthol cigarettes are associated with an earlier age of initiation.

There is also very limited data on whether the early use of menthol cigarettes is associated with subsequent nicotine dependence. There is inconclusive data from the two studies that we saw

on switching patterns between menthol and nonmenthol cigarettes. And then, the published literature documents industry awareness of menthol cigarettes appeal to newer smokers.

As we're going to hold off then on the questions --

DR. SAMET: Right. So thank you, Josh. What we're going to do is move on to -- if Dr. Hoffman is ready, move on to her first presentation. Then we will take a break after that.

So the next presentation will be Menthol Cigarettes and Nicotine Dependence.

DR. HOFFMAN: Good afternoon. Thank you for staying with us. Thanks to the members for being apart of the Panel. I know you heard thank you a lot today, and probably will continue to hear it. It's a big job, and we appreciate it.

My name is Allison Hoffman. I'm currently at the National Institute on Drug Abuse; but I am on detail at the FDA Center for Tobacco Products.

As all the previous presentations today, these presentations are based on literature review

done by the NCI. The current topic of menthol cigarettes and nicotine dependence is based on 31 articles.

The time to first cigarette upon waking is considered a really robust indicator of nicotine dependence. So the shorter the time from the time you wake up until the time you light your cigarette, the more dependent you are considered.

One study by Ahijevych and Parsley of 95 female smokers found that those who smoked menthol had significantly shorter time to the first cigarette as compared to the nonmenthol smokers. This is significant. Menthol smokers smoked their first cigarettes an average of 19 minutes after waking up; whereas, the nonmenthol smokers made it twice as long, at about 37 minutes after waking up.

Night waking to smoke is also considered an indicator of nicotine dependence. In this case the smokers wake up at night and smoke, and then go back to sleep. This is not waking up for the day to smoke.

Menthol smokers had a greater incidence of

night waking to smoke as compared to nonmenthol smokers. Almost 60 percent of menthol smokers in this study reported waking up at least once to smoke, and then went back to sleep. That compares to about 45 percent of the nonmenthol smokers.

Now, the night-waking smokers had significantly shorter time to first cigarette upon waking, which means that even though there had been less time since they last smoked, because they woke up during the night to smoke, they actually smoked much more quickly. So about 70 percent of the night wakers smoked within the first five minutes of waking up; and that compares to about 28 percent of the nonnight-waking smokers.

Cigarettes per day is often used as an indicator of nicotine dependence. There haven't been that many studies to date that actually compare menthol smokers versus nonmenthol smokers. There have been many studies that have compared Black smokers with White smokers. Black smokers are much more likely to smoke menthol cigarettes. In many of these studies menthol is not considered as an

independent factor.

The data are split. Two studies found that there was -- that menthol smokers smoked fewer cigarettes per day as compared to nonmenthol smokers. And two studies failed to find any significant difference in cigarettes per day. So there is no clear relationship between the type of cigarettes that someone smokes, and the cigarettes per day.

I should note that there have -- there was a study by Okuyemi, et al. that found that menthol smokers tended to smoke cigarettes with higher nicotine, 1.2 milligram as compared to one. So that might be a possible reason for this.

Now, cigarettes per day, there are some issues with it. One of the issues is restrictions on smoking. And so one of the things that's happened over the past ten years is that we have had greater restriction in where people are allowed to smoke. Whether people are allowed to smoke in restaurants, whether they are allowed to smoke in public buildings, whether they are allowed to smoke

outside buildings. So there are some issues with using cigarette per day as an indicator of nicotine dependence.

The Fagerstrom Test for Nicotine Dependence is an accurate composite of individual questions, including time to first cigarette, as well as cigarettes per day. There have been a couple of studies that have compared the Fagerstrom scores of menthol smokers versus nonmenthol smokers. So the higher the Fagerstrom, the higher the dependence.

Menthol smokers were no different than -- menthol smokers were no different than nonmenthol smokers when it came to the Fagerstrom score. As I mentioned with the previous slide, cigarettes per day, there are some issues with these questions. Cigarettes per day actually account to 30 percent of the Fagerstrom. So when interpreting Fagerstrom scores, it's important to keep that caveat in mind.

Next, we're going to discuss menthol and nicotine dependence in youth. According to two waves of the National Youth Tobacco Survey, which

was done for grades six through 12, one study found that teens who regularly smoked menthol cigarettes had a 45 percent greater odds of scoring higher on a nicotine dependence scale for adolescents.

Now, this Nicotine Dependence Scale for Adolescents was trying to be sensitive to some of the differences in scheduling of youth versus adults. For example, it differentiated between the first cigarette a day on a weekday, and the first cigarette a day on a weekend. So again, the menthol smoking adolescents were more likely to score higher on this measure of nicotine dependence.

There were other symptoms of nicotine dependence that were assessed using the same data set. When compared to youth smokers of nonmenthol cigarettes, smokers of menthol cigarettes were significantly more likely to report needing a cigarette less than an hour after smoking, and also to experience craving after not smoking for a couple of hours.

In a 2006 survey that was reported on by Mullenberg and Legge, there were almost 2000

secondary school students that were surveyed. When compared to nonmenthol smokers, the menthol smokers were more likely to report smoking more total cigarettes during their lifetime, were more likely to smoke more days per month, were more likely to have a shorter time since their last cigarette, and also more likely to have become a daily smoker.

Now, of those students it turns out that the Black menthol smokers had the highest risk in all four of these categories. So they had a -- they tended to smoke more cigarettes in their lifetime, as well as more days per month, shorter time since their last cigarettes, and also more likely to become a daily smoker.

In this study by Collins and Moolchan, which was conducted in Baltimore -- it was a smoking cessation study. Smokers that smoked menthol -- adolescent smokers that smoked menthol were more likely to smoke earlier in the day upon waking up. This is time to first cigarette. And that parallels with what we found in the adult literature. So as you can see, almost 50 percent of the adolescent

menthol smokers smoked within the first five minutes after waking up. That compares to only about 30 perfect of the nonmenthol cigarettes.

With the Fagerstrom, it's also administered to adolescent smokers. In the same study there were no differences in the Fagerstrom score when the adolescent menthol smokers were compared with the nonmenthol smokers. This parallels the finding in adults.

Again, as with the caveat with cigarettes per day, Fagerstrom for the adult population. In youth, this may be even more of an issue, as there are restrictions in school, in school activities; it is illegal for them to be smoking. So there are issues when you try to interpret the Fagerstrom and cigarettes per day for adolescents in addition to adults.

What is one possible mechanism for the behavioral differences? We're going to discuss briefly one such mechanism is nicotine metabolism. What you see before you is a schematic of how nicotine is metabolized in the body. Basically, how

it's broken down and activated by your body.

Nicotine is the main addictive component of tobacco. What you see on the top is -- is the metabolic pathway, and this is in the liver. What you see is nicotine is metabolized by an enzyme called 2A6 in the liver, and it is metabolized into something called cotinine. Cotinine is them further metabolized into hydroxycotinine. Now, both nicotine and cotinine are metabolized by the same enzyme, this 2A6 enzyme.

The idea is that slower metabolism means that nicotine stays in your body longer. Usually, this is measured with cotinine, because the half life of nicotine is only two to three hours. The half life of cotinine is ten to twelve hours. So cotinine is used as sort of a proxy for nicotine, because it's easier to measure.

So what menthol does is it can inhibit 2A6 activity, which means that nicotine is active longer. You will notice that glucuronidation, along the lower pathway, is also inhibited. Glucuronidation is considered a minor metabolic

pathway for nicotine. However, it may become more important for people who are genetically slow metabolizers with variants of the CYP 2A6.

When we look at cotinine levels measured either by absolute levels of cotinine, for example, in urine output, or as a measure of half life, we see sort of a mixed pictures of data. What you see are -- in some studies you see that menthol smokers have reduced nicotine metabolism. In some you see that there are no significant difference; although, in two of those studies it was a trend toward reduced nicotine metabolism. That trend failed to reach significance.

Then you have two studies which the menthol smokers were no different in their cotinine -- or in nicotine metabolism as compared to nonmenthol smokers. So it's a mixed bag. But going with this data, what can we hypothesize is the relationship between nicotine metabolism and dependence?

Well, one hypothesis is that the people who have higher nicotine levels may be more

sensitive to smaller fluctuations of nicotine; and therefore, they may be more susceptible to withdrawal. So they are smoking to alleviate withdrawal symptoms. Some data for this may be time to first cigarette of the day, and night waking to smoke. So when their bodies get below a certain level of nicotine, there is the drive to alleviate the withdrawal.

Another hypothesis or the flip side of that is slow metabolizers may actually be less dependent, and more likely to quit. So there is less variation in nicotine, because nicotine is being metabolized more slowly. You don't get large fluctuation. There are some issue around skewing of the sample. So in many cases it is very difficult, for example, to find White male menthol smokers; whereas, you may have an abundance of Black female menthol smokers. So it may be skewed based on race/ethnicity, or by gender.

So in summary, there are some behavioral evidence for menthol cigarette smokers being more dependent. This includes time to first cigarette in

both adults and in youth. Night waking to smoke -- this is in adults; as well as other measures, nicotine dependence. These were some of the youth measures that were discussed.

There were two indicators that suggested a lack of evidence that menthol was associated with greater nicotine dependence. That includes the cigarette per day, as well as the Fagerstrom Test for nicotine dependence. Those are in youth and adults. And we discussed one possible mechanism for some of these differences, which are the effects of menthol and nicotine metabolism.

So thank you very much. Are their clarifying questions now?

DR. SAMET: I think, actually, we will wait until after your next presentation to do clarifying presentations (sic) for Josh's last, and your first two.

DR. HOFFMAN: Okay.

DR. SAMET: So what we're going to do is take a break until 2:30. So roughly 15 minutes, and we will reconvene then.

(Whereupon, a recess was taken.)

DR. SAMET: It's 2:30. So let's get started, if everyone would take their seats, please.

Okay. So just as a reminder, we're going to go ahead and hear the next presentation by Dr. Hoffman; and then, we're going to have clarifying questions.

DR. HOFFMAN: Welcome back from the break. Thank you for sticking with us. I am still Allison Hoffman.

My next presentation is going to be on Menthol and Smoking Cessation Behavior. You are going to have major de ja vu. Same bibliography that we've been talking about. This one is based on 12 articles.

As an overview on what I will be speaking today. What role, if any, does menthol play in smoking cessation and treatment outcomes in adults? What interactions, if any, does menthol have with race/ethnicity in smoking cessation success? And finally, what role, if any, does menthol play in smoking cessation and treatment outcomes in youth?

So we will start with adults. There have been several studies that have found no association between menthol smoking and quitting. Among these was a large scale telephone survey of over 13,000 people that was conducted in 1998, and again in 1993.

It was a cross sectional analysis of case control data from a study conducted on more than 19,000 current and former cigarette smokers; and there was a cross sectional survey of 480 Black smokers where no difference was found in lifetime quit attempts.

In a 2004 study by Okuyemi, there was a cross sectional survey of 480 Black smokers. The menthol smokers had significantly less time since their last quit attempt. Menthol smokers had an average of 12 days since their last quit attempt, versus 24 days with the nonmenthol smokers.

There were trends that were not significantly significant for shorter durations of abstinence for the longest ever quit attempt in menthol smokers; and also menthol smokers having the

shorter, more recent quit.

In this 2003 study by Okuyemi and colleagues, there were 600 Black smokers that participated in a smoking cessation study. They received either placebo or bupropion, which is a pharmacotherapy that is considered efficacious for smoking cessation. Bupropion did increase abstinence at six weeks, and that's what you see circled -- that's not working too well. This is what you see circled.

So bupropion was effective at increasing abstinence rates at six weeks. That's the end of treatment for the bupropion. What you notice is that the menthol smokers had significantly poorer outcomes with the bupropion. So you have an interesting interaction between bupropion being efficacious for increasing cessation success; however, it is less efficacious for menthol smokers.

In this study by Harris, et al., they were trying to predict cessation success among Black smokers. This had about 535 smokers. Their outcome was seven day abstinence with pharmacotherapy of

bupropion. At week seven was the end of treatment. So after seven weeks of treatment, bupropion did significantly increase success in quitting. By doubling it, essentially 41 percent were able to remain quit, as opposed to about 21 percent for those who got the bupropion placebo.

With menthol versus nonmenthol smokers, we see the same -- we see a similar story as on a previous slide where menthol smokers had significantly poorer outcomes as compared to nonmenthol smokers. So menthol smokers on average only were abstinence -- only 28 percent of menthol smokers were able to maintain abstinence for the seven days post treatment. Whereas, nonmenthol smokers were able to maintain abstinence at a rate of about 41 percent.

There was no treatment by race or ethnicity interaction that was common in this study.

In another study by Okuyemi and colleagues in 2007, 755 Black smokers who were light smokers -- said that they smoked ten cigarettes or less per day -- were given one of several treatment options.

One was placebo or nicotine gum. Another group got nicotine gum. Another group got health education; and another group got motivational interviewing plus counseling.

And what you see here is seven day abstinence at 26 weeks post treatment. And the menthol status is in the white lighter bars, and nonmenthol is in the darker bars. What you see is across the board the menthol smokers did more poorly as compared to the menthol smokers (sic). That was significantly so in two of the groups, the nicotine gum group, as well the health education group. So cessation success was reduced by menthol.

In a study of female -- female prisoners who smoked. After a ten week intervention that was group psychotherapy plus a nicotine replacement patch, menthol was not associated with quitting success at 12 months follow-up. Again, these were incarcerated women. So there were a couple of caveats. One is that menthol smokers were labeled as menthol based on their smoking while in prison. That may have changed from prior to being

incarcerated. So someone who may have smoked menthols prior to being incarcerated, they have switched to nonmenthols while in prison, and vice versa.

There were also very uneven sample sizes. For example, there was an extremely small group of Black nonmenthol smokers. The vast majority of Black smokers -- the vast majority of Black smokers were menthol smokers.

Next, we're going to discuss ethnic and racial differences in adult smoking cessation. In a secondary data analysis that was done from a multisite randomized trial, which pulled smokers from VA medical centers, as well as pharmacies failed to find any significant differences in abstinence rates when comparing menthol versus nonmenthol smokers. They also were failed to find any race or ethnicity differences in abstinence rates.

A second study of over 1500 Black and White smokers also failed to find any difference in quit or relapse rates when looking at menthol versus

nonmenthol smokers. They also failed to find any significant ethnic or racial differences in these samples.

In this 2009 study by Gandhi, et al., you see a graph illustrating seven day point prevalence abstinence at four weeks post treatment; and it's broken down by race/ethnicity. The first bar is all smokers, broken down by menthol and nonmenthol; followed by menthol versus nonmenthol in White smokers, Black smokers, and Hispanic smokers.

What you see is that across the board menthol smokers did more poorly as compared to nonmenthol smokers. So the White smokers, the Black smokers, and the Hispanic smokers who smoked menthol had poorer outcomes as compared to their nonmenthol smoking cohorts.

Of all of the groups, the Black menthol smokers did worse when you look at the six month outcome. So there was a significant race by menthol interaction.

Using data from the 2005 U.S. National Health Interview Survey, of over 7800 smokers who

had made quit attempts, overall, menthol smokers were less likely to be former smokers as compared to nonmenthol smokers. So if you look at former smokers, menthol smokers certainly had about a 57 percent chance of being a former smoker, as compared to the nonmenthol smokers who had a 61 percent chance. This is a significant difference.

When looking at ethnic or racial differences, Black and Hispanic menthol smokers were significantly less likely to be former smokers as compared to the nonmenthol smoking counterparts. Black menthol smokers had about a 44 percent chance of being former smokers, as compared to their nonmenthol group at 62 percent.

A similar pattern is seen with Hispanic smokers. Hispanic menthol smokers only had a 48 percent likelihood of being a former smoker, as compared to 61 percent for their nonmenthol smoking counterparts.

There were no differences between White menthol and nonmenthol smokers. Both of these groups had a 61, 62 percent likelihood of being

former smokers.

What about menthol cessation and youth? There was no information on quitting success that compared menthol to nonmenthol youth smokers. The closest we could come was a study that looked at the National Youth Tobacco Survey. Of over 3,000 teen smokers in 2002, this study found that adolescent menthol smokers were significantly less likely to be seriously thinking about quitting. However, the good news is that those who did try to quit were significantly more likely to have sought help in quitting. This includes going to school programs, going to internet cessation sites, calling the quit line, or participating in other cessation group activities.

In summary, there were several studies that found no association between adult menthol use and cessation. This includes a national survey of self-report, a local and regional survey with self-report, a longitudinal study with self-report; and there was a clinical study, as well as a secondary data analysis of large scales randomized

intervention study.

However, there were also several studies that found that adult menthol smokers have lower levels of successful quitting as compared to nonmenthol smokers. This included clinical studies of both moderate to heavy smokers that smoked at least ten cigarettes per day, as well as light smokers who smoked less than ten cigarettes per day.

It also showed that efficacious treatment, such as bupropion, nicotine replacement gum, as well as some counseling were less efficacious in menthol smokers, as compared to nonmenthol smokers.

Another study that found that adult menthol smokers had lower likelihood of being former smokers was the national survey, the NHIS.

There may be an interaction between ethnicity and race, and menthol. For example, there were two studies that found worse outcomes for adult Black and Hispanic menthol smokers. They were less likely to remain abstinent; and also less likely to quit. It was inconclusive for adult menthol smokers.

I think with that we go to clarifying questions.

DR. SAMET: Right. So we're going to have clarifying questions for the last three preparations. Josh, you might want to be available as well. I almost feel like saying, somebody who doesn't want to comment, raise your hand. We're going to start with Mark -- Melanie.

DR. WAKEFIELD: My question is for Josh; and it relates to your presentation on initiation. And I just was focusing on the slide which looked at menthol cigarette use over time by youth smokers aged 12 to 21. Just that remarkable sudden change between 2007, 2008, which could just be sampling variation. But that is exactly the kind of thing that points to the need for us to have better access to data on pricing, marketing, and so forth; and to try interpret some of these trends.

For example, I know that, you know, there is scanner data available that have been used by various people to look at price discounting over time, and so forth. That's the kind of thing that

FDA maybe should consider getting access to.

DR. SAMET: Response, Josh.

DR. RISING: Yes. In general, there was not a wealth of information that we were able to incorporate into the presentation. So any other source of information, we will definitely add to that.

DR. WAKEFIELD: I think, just as a follow-up, the presentation on marketing and the presentation on initiation were characterized by having little information available. And I mean, I think it's just really important to remind ourselves that there is huge literature on the relationship between tobacco advertising and promotion, and tobacco and consumption, especially in relation to how it's causally related to youth up take. So I do think we need to sort of bear that in mind. It is not really a question; I suppose a comment.

DR. SAMET: Okay. Jack.

DR. HENNINGFIELD: Thank you. There is three areas that you have covered, initiation, dependence, and cessation; and I have a question

that's really the same for all of them.

In all of these -- each of these areas each of you show one or more studies that show no, what I will call, adverse effects, like increased initiation. And one or more studies that showed the increased adverse affect. And I'm trying to get a sense -- I approach this not thinking what's right or what's wrong; they are documented. So I'm trying to get a sense of what information you also had that you didn't have time that would bear on that?

So Dr. Rising, on the switching, in the Kaiser study found four times -- people were four times more likely to switch to menthol than the other way around. Depending on the extent of that, if that's at the expense of cessation, then that's a serious public health concern. But the other study show no affect.

So is there any information that gives us an idea of what is happening in the population, how frequently people switch; and if switching is at the expense of cessation?

DR. RISING: Yes. So very good questions.

In general, not tons of information on that. Kind of other caveats I would give with that information is, you know, so that study data was from 1979 to 1986. So how relevant that is to what's going on with adults smoking menthol cigarettes today, you know, definitely kind of an open question. You know, we know that -- yeah, so open question. And, certainly, we need some more information on that.

As to other kind of evidence, you know, we're kind of comparing the two. You know, I think it's very difficult to try to make comparisons as to this, you know, is a better study than the others. Compared to some other studies that we reviewed, you know, certainly both of those were relatively robust in terms of descent period of time for follow-up, pretty good sample size, you know, certainly compared to some of the other data that we have that were dozens of, you know, individuals. Those were both thousands of people who were being followed. They were overall better quality of studies than some others.

DR. HENNINGFIELD: That was impressive.

This is -- I kind of throw out this because there will be others that will be presenting other sources of information; but this will be an area that I think we're going to need -- there has got to be information. We're going to have to find where it is.

Similarly, Dr. Hoffman on initiation there was evidence -- and I forget which ones now -- one or more of the increased risk for dependence development; and others where it was not as clear.

So my question is the same -- and I have the same question related to cessation. And if you look at your summary at the end, you know, there is some studies that show delayed cessation. Others that show no effect. And obviously, these are pretty public health concerns, because if you smoke longer, that's harmful.

DR. HOFFMAN: Right. Well, in many cases if you are comparing a group of menthol smokers to nonmenthol smokers, you are pulling from a sample of convenience. They are very uneven. Like I said, it's very unusual to find, you know, White male

menthol smokers. So what you might have is a skew. Many of the studies use Black smokers, for example. Very high -- relative preference for menthol cigarettes.

And so what you have is sample size -- you know, groups that aren't very even. Some of the groups fairly small. In many of these cases you can have, you know, 500 people included, but 400 of them may be menthol smokers. You know, so that's -- so not only do you have sort of a gender skew, you could have a racial/ethnic skew.

You know, in terms of treatment, most studies don't separate out menthol as an independent factor, so we just don't know. The two studies that I mentioned look at bupropion. I think those were the only two that looked at bupropion. There was one that looked at sort of a combination of -- there was one that looked at, you know, behavioral treatments plus pharmacotherapy; and there was one that just looked at just pharmacotherapy. They are so -- there aren't that many. So it's very difficult to draw conclusions.

Each one may use different treatment regimens. Some may treat for six weeks. Some may treat for seven. Some may give abstinence rates at 12 month follow up; some may give abstinence rates at end of treatment. It is very difficult to draw direct comparisons as to which one might be a stronger study, except by falling back on what do your sample -- what does your sample look like.

DR. HENNINGFIELD: You may have answered my last question, but let me clarify. Because I'm looking at if menthol has the effect on some population of increased initiation, dependence, or delaying cessation that is an -- an adverse effect, is one way of looking at it. So I'm trying to figure out what is the overall population effect; and also, is there subpopulation?

For example, the way you presented it, it appeared that the transition to dependence was particularly strong in the younger African American sample. The apparent impediment to cessation appeared particularly strong in an African American population. So one of the things I'm trying to

figure out is, is -- did I get that right? And if so, maybe we have an effect where the main AE, adverse effect, is in certain populations.

DR. HOFFMAN: Yes.

DR. HENNINGFIELD: So anything that you have that bear on that -- because if it's not there, then, maybe that's another thing that we have got to try to get from the industry, or other surveys from other sources.

DR. HOFFMAN: I think that's an excellent point. When it comes to particular subpopulations of -- subpopulations, you have the most on Black smokers. There is very little on Hispanic smokers, for example; and that may be an important population to look at, as well as other populations that aren't currently represented in these.

But I think you hit the nail on the head. I think that we need to look at different populations both in their evidence seeking dependence, as well as their response to cessation. I don't think that you can look at all menthol smokers as one group. I think the way you are

really going to find differences is by splitting among gender lines, among racial/ethnic lines; find out which population you are looking at, and then looking at how you can tailor treatment to them.

DR. HENNINGFIELD: This is very helpful. Thank you.

DR. SAMET: I'm going to take Chair's prerogative. I think somewhere back -- about three questions back in Jack's series -- this would be another comment disguised as a question. In this series of presentations, up to including these Manza studies that are rather small and characterized as statistically significant or not -- and I guess that I would ask that you consider more informative ways to express the findings up to and including, if appropriate, the possibility of summarizing quantitatively across studies.

DR. HOFFMAN: I think it's very difficult to summarize quantitatively across studies. There aren't that many there.

DR. RISING: I think the other thing about that is, I think we tried to point out when there

were particular methodological issues that were associated with some of the studies. I think we did try to discuss a little bit some of the limitations.

DR. SAMET: I appreciate that. I think maybe we will have some additional discussion tomorrow about the best way to present findings beyond significant, nonsignificant I think. Next, Neal.

DR. BENOWITZ: Two questions. The first one is like Jack's, but specific -- the two large studies, the Hyland, Muscat study I found no difference. Can those be reanalyzed specifically by race? Because the race menthol interaction, I think, is very provocative. And it is quite possible, since most menthol smokers in the general population are Whites, that you could have missed that effect if you are looking at 13 or 15,000 people as representative of the population. I'm wondering if those data sets could be reexamined in terms of looking at African Americans.

DR. HOFFMAN: I don't see why they wouldn't be able to do that; but I'm not familiar

with their particular data set, how it's coded, and how it's classified. It would seem to me they should be able to do that.

DR. BENOWITZ: Okay. The second question is, in the Pletcher study one of the really interesting findings, I thought, was that there was an effect of menthol on relapse. That was a study that followed -- which had multiple assessments over time. It wasn't the bias of memory that actually assess people at different times.

Quitting was not different, but relapse was different in menthol; which has the same effect. This means that fewer people are quitting permanently. So to the other studies -- can we look at relapse in other databases?

DR. HOFFMAN: I would think that you could. I think one of the -- take a step back. One of the issues of snapshots of whether you quit in the last six months, for example, has to do with, you know, how many times someone has quit. So what we saw with the menthol smokers in one of the studies, it was only, you know, 12 days since their

last quit attempt, versus 24.

So if they are making more quit attempts and you happen to catch them in the middle of one of those quit attempts, that might be classified differently than if you had taken the same subjects and asked them one week later. But I think that -- that -- the points you are bringing up are well taken.

DR. SAMET: Ursula.

DR. BAUER: So we've heard some fairly equivocal data, I think, all day in terms of the conclusions that we can draw. I think we heard this morning that there is potentially more advertising directed at menthol smokers, potentially more use of promotion; which could mean, I suppose, that there are more promotions available to menthol smokers. Menthol smokers might have more -- lower incomes; and potentially might be more dependent smokers. So all of those things, of course, influence quit success and potential for relapse.

Is there a way to control -- have the studies -- can the sturdies control for some of

those things so that we can understand what's menthol -- what's the effect of menthol itself versus what's the combination of factors that are kind of wrapped up in a menthol smoker?

DR. RISING: So it seems like, to rephrase the question you are asking me, what's really the overall net impact of menthol in cigarettes. Is that what you are trying to get at?

DR. BAUER: How do you explain that with some of the studies that we're looking at?

DR. RISING: Yes. So they are very good questions. I certainly don't have the answer to that. I think to a large degree it's up the Committee to try to synthesize at lot of this information and come to some conclusions based on that.

DR. BAUER: Just a follow-up to a comment, Dr. Hoffman, that you just made. I think we learned this morning that, in fact, there are more White male menthol smokers than there are Black male menthol smokers. So why would it be so hard to find the White male menthol smokers?

DR. HOFFMAN: I think if you are looking at an overall general population it wouldn't be. The studies that we're including possibly they are samples of convenience. You know, the prisoner samples or the adolescents that come into the cessation clinics.

It just so happens that when there is an uneven distribution of menthol by nonmenthol, I can't think of a single study in the bibliography that I looked at that didn't skew towards -- in the same direction I just mentioned, so away from White men menthol smokers towards Black -- especially black female smokers. Just the way that the studies have -- you know, how the cards have fallen.

DR. SAMET: Dr. Clark.

DR. CLARK: Thank you for the presentations. When you look at menthol smokers being treated with bupropion, is there a possibility of menthol interacting with the bupropion?

DR. HOFFMAN: I guess there is; however, the studies that have been done that have specifically tried to look at racial or ethnic

differences in the program have failed to find differences. Also, if you look at the studies that look at other kinds of medication, for example, the nicotine replacement gum, which is also pharmacotherapy therapy, you get differences across racial and ethnic populations.

Does that answer your question?

DR. CLARK: No, actually it doesn't. I think the Committee will have to address that question. It does raise the question -- since the previous speaker pointed out that menthol does interact with metabolism of nicotine, it might interact with metabolism with other substances, not just nicotine. The question is, does it interact with common medications? And bupropion question is present.

In part, because, as you pointed out, these convenient samples look at convenience population, it's probably harder to find African American populations that don't use menthol than it is to find African American populations that do. So there may be a difference in the population of the

people that present.

Two issues in terms of interaction; one, the medication effect. So that would raise a question -- hypertensive medication and other medication. If there is no interaction there is none; but that issue has already been addressed in part by menthol's effect on nicotine metabolism.

DR. SAMET: Greg.

DR. CONNOLLY: Thank you.

Josh, you know, I'm intrigued also, as Melanie is, with the decline in the SAMHSA data, the NSDUH data from 2007 to 2008. I have two questions to that. One, did you look at, again, brand use? Did you factor out a dedicated menthol brand use over that time period to see if there is a variation between one brand than another? That may relate to issues of marketing. It may relate to issues of content, both in the broad and in the smoke. It may relate to other issues.

The second question is -- so that's one. The second question is, when will the 2009 data be available? Will that be available for the Committee

prior to completion of this activity?

DR. RISING: Let's see, so the first one -- so we did not look at brand specific information. We kind of looked, again, at the aggregate, you know, do smoke menthol or nonmenthol? We certainly could try to return to the data and look at it in that way.

And the second, when it's going to be available; I do not know that offhand. There may well be some other people who do.

DR. CLARK: What survey?

DR. RISING: The survey that the 2004, 2008 data was based on.

DR. CLARK: The 2009 survey will be available in September; that's when it's disclosed. The raw data will be available a couple months later. So this year we will be doing roll out in September, and then the THS will be available subsequent.

DR. CONNOLLY: Thank you.

And then, Allison, just a few questions. I have to say I was, quite frankly, impressed with

the studies that looked at use of medications and relapse. And Dr. Clark, I don't know, maybe we should put menthol in bupropion, I don't know.

But this goes to Josh's point. We're new; we're taking a first cut at this. I think you are doing an excellent job. Everyone should be congratulated for work they have done.

Ultimately, the Committee has to weigh this science. I think John was saying, let's make it objective as possible. I think if we had a standard format for comparing, you know, and describing what we think are, you know, stronger studies versus weaker studies, that would make the work of the Committee easier. I heard a comment, well, that's the Committee's job. I sort of got very worried when I heard that. So that's just sort of a comment.

But what goes into that, because I realize FDA now is going to require reporting of additives to tobacco products under the statute. There has been regulations promulgated, and there will be reporting deadlines. But what this conversation

today is speaking to you can almost describe as post marketing surveillance activity of drugs. We have been looking at epidemiology, behavioral studies independently of the manufacturer.

I think it would be important to know better in the reporting activities of the FDA unit the characterization of menthol, the levels of -- particularly by brand, both in the broad and in smoke. Then we would better handle the characterization of the product itself. And I don't see that as your job. I think your job has been -- you have done a very good job in looking at the behavioral and the epidemiology use. I think that's something that should be considered.

Then, Allison, I think your presentation, again, I think on addiction was excellent. You focused, you know, very heavily on behavioral and some epidemiological studies, and then metabolism of nicotine. More and more literature is looking at the issue of chemosensory effects, particularly of nicotine on the head and neck receptors. And I was curious if you looked at any data of the

relationship between nicotine effect on the head and neck receptors, specifically the trigeminal receptors in menthol. Is menthol affecting those same receptors? Is there competition?

So again, I'm trying to go from the characterization of the product to the clinical effects of the product, to the post market surveillance of the product. And I listened very carefully yesterday to the role of the Committee. So I'm trying to look at this as any other committee would look at data presented by a drug manufacturer. And I would be curious about the chemosensory effects; and have you looked at that, the reaction of nicotine and maybe the related action of menthol.

DR. HOFFMAN: In terms of the bibliography that we were working with, we were trying to focus primarily not on the articles that characterized menthol just independent -- as independent chemical entity, but as it interacted with the tobacco smoke.

There were articles that looked at the chemosensory effects of menthol. From what I can recall -- and I would have to go back and check --

those were not in conjunction with any kind of nicotine and tobacco smoke. Because it was menthol as an independent entity, it was not included in this. Does that make sense?

DR. CONNOLLY: It does. And maybe this we will discuss tomorrow. My impression and understanding is that there is an increasing body of literature that speaks to the chemosensory effects of nicotine on head and neck receptors. I am just curious if, one, you have looked at that at NIDA.

And then, number two, is there a relationship between those chemosensory effects with nicotine and with menthol on those same receptors? We had a discussion this morning of thermal receptors. I think there are other receptors that could be interacted with that are -- that I'm just curious if you have looked at that at NIDA.

DR. SAMET: Greg, I think, actually this question, and your ultimate question, probably are for tomorrow questions. I think you are sort of calling for other data beyond the scope of what was presented. I think we moved beyond clarifying. I

think hold those thoughts for tomorrow. I think I will move on to Dorothy.

DR. HATSUKAMI: My comments are similar to what Jack and Neal had brought up. In the study -- Dr. Hoffman, in the study on dependence measures and the effects of menthol on those measures, did they control for the confounding effects of race? I don't think you really -- I know that some studies did take a look at that -- take a look at race and -- racial/ethnic differences; but in the other studies did they control for?

DR. HOFFMAN: So could you just repeat -- because they controlled for various demographic factors, which included that. They also controlled for smoking behaviors. So -- number of cigarettes per day. In many cases, the amount of cigarette that was smoked. So I think that would be included in the demographic factors that they were controlling for. I am not sure that was your question.

DR. HATSUKAMI: Yes, I was wondering if they controlled for racial/ethnic differences?

DR. HOFFMAN: In many cases they did.

DR. HATSUKAMI: They did or did not?

DR. HOFFMAN: They tired to, yes.

DR. HATSUKAMI: All right. Another question I have is, are there animals -- did you run across any animal studies that looked at the effect of menthol on the acquisition, extinction, or reinstatement of nicotine self-administration if you combine menthol with nicotine versus nicotine alone?

DR. HOFFMAN: I did not come across any of those articles in the bibliography.

DR. HATSUKAMI: And then, Dr. Rising, I have a question for you. Are there any survey datas that might be available -- survey data that might be available to examine individuals that might experiment with menthol versus nonmenthol cigarettes that will eventually go onto daily smoking? See if there is any differences in terms of percent that go onto daily smoking.

DR. RISING: Yes, in general, that was not kind of assessed. You know, there was one longitudinal study of seventh graders that followed

them for about 30 months or so. So again, very small sample size. That was the only one that sort of had any longitudinal components to see about the impact of menthol. Certainly, the vast majority of the data we have is really cross-sectional data. So it would be difficult to drive those longitudinal trends.

DR. SAMET: Okay. Mark.

DR. CLANTON: Both of you present studies that show differences or might even be called equivocal. We had other studies presented in the same way. I want to offer up to the Committee, we may want to be very careful about calling studies that show different results "equivocal." The reason may have to do with genetics of biology. So the cytochrome or the mitochondrial enzyme system that metabolizes drugs, we know there are genetic differences person to person within a race, and certainly between races. So nicotine metabolism may be different depending upon how your cytochrome enzymes are being expressed.

On the bupropion example, which I found

really curious -- bupropion is less effective in African Americans smoking menthol. I wasn't clear why that happened. So it may be either cytochrome differences creating different metabolisms of the drug bupropion as well.

So we may need to be really careful about simply calling something equivalent when, in fact, there may be some clear genetic reasons for why the drugs are metabolized differently producing different results.

DR. HOFFMAN: May I comment on that. I think that you are bringing up a very important point, and it's definitely well taken.

Most of the studies that looked at racial and ethnic differences really only looked at White versus Black. You know, the few studies that looked at -- for example, Hispanic smokers with the bupropion found that everybody across the board had poor outcomes if they smoked menthol.

Now, I mention that the six month follow-up for that study, rather than six weeks, which was on the graph, where every ethnic and

racial menthol smokers did more poorly, the Black smokers that smoked menthol did significantly worse. However, there was a trend for the Hispanic menthol smokers as well that failed to reach significance. So it's a point that's very well taken, and it is critical for interpreting somebody's data.

DR. SAMET: Patricia.

DR. NEZ HENDERSON: This is just a follow-up question actually to Mark, and in terms of genetic variation among nicotine metabolism, among different race groups, whether or not any of the studies that are being done right now are looking at that.

DR. HOFFMAN: In terms of what was in the bibliography, there were very, very few that looked at that in relationship to menthol. So there were studies that looked at genigrations (phonetic) in metabolisms, but we only included it if it was related to menthol.

DR. SAMET: Okay. Anyone else with comments?

Okay. Dr. Hoffman, move on to your last

presentation.

DR. HOFFMAN: Okay. This is my third, and you will be happy, final presentation of the day. This presentation will be on the Possible Health Effects of Cigarette Mentholation.

This presentation is based on 65 articles that was pulled from the bibliography of literature research in January.

We're going to be covering quite a bit. We are going to start with introduction to menthol; biomarkers of tobacco smoke exposure; toxicity and cellular effects; respiration; cardiovascular function; allergic reactions and inflammation; tobacco-related disease, as well as some discussion before the summary.

So introduction to menthol. This is going to be a very brief introduction. We have already discussed that menthol is found naturally in peppermint and cornmint oils. It is a saturated cyclic monoterpinoid alcohol. I put this up here -- if there are any chemists in the audience, I put it out there for you. These are four different ways of

showing you the chemical structure of menthol.

Next, I'm going to talk about some of the biomarkers of tobacco smoke exposure. By far, the most common biomarker is cotinine, which I mentioned earlier is used to measure nicotine. Since we already discussed that in the talk on nicotine dependence, that is not going to be included in this talk. Instead, we're going to start by talking about carbon monoxide.

When someone inhales tobacco smoke, there is an increase in carbon monoxide. That can be measured either with sort of a breathalyzer, exhaled carbon monoxide; or it can measured in an increase in carboxyhemoglobin. So what I have here compares menthol smokers with nonmenthol smokers. So both of them have increases in carbon monoxide. It is just done relative to each other, if that makes sense.

So we have one study by Ahijevych that actually found that relevant to nonmenthol smokers, menthol smokers actually had a decreased carbon monoxide. This was actually a women only study; and this was only true for the Black menthol smokers in

the studies -- only true for the black women in the study.

There were several that found no difference between menthol smokers and nonmenthol smokers; and there were three that found that menthol smokers had increased markers of carbon monoxide as compared to nonmenthol smokers.

However, you will notice that one study is listed twice. It is listed both in the no effect column, as well as the increased carbon monoxide column. That's because in the increased carbon monoxide column, they found a borderline significant difference in carboxyhemoglobin. However, the same study failed to find a significant difference in an exhaled carbon monoxide. So the same study, two different measures, two different findings.

Why are the data kind of inconsistent? Well, there are some potential physiological variables. The mucous layers and mucosal cold nerve endings can make a difference. Differences in how the cigarette burns. So menthol in mainstream smoke may be reduced depending on how the cigarette is

burning, the pyrolysis. There could be other chemicals present in the smoke that can affect carbon monoxide.

Tobacco specific nitrosamines are known carcinogens. The two that we are going to be discussing today are NNAL and NNK. Both are present in tobacco smoke.

Menthol inhibited metabolism of NNAL in human microsomes in vitro. So this was basically in a glass tube of microsomes, and you added menthol once -- after they had been treated with NNAL. And the menthol inhibited metabolism of NNAL; which means the NNAL was essentially staying around longer.

Now, when menthol was administered to NNK-treated rats, there was an increase in NNAL metabolites, which suggest the exact opposite. It suggest that in this hole NNAL model nicotine actually enhanced metabolism. So you have the in vitro finding, and you have the in vivo finding.

The big question is, what does it do in people? What I have here is a comparison of two

studies that ask the question, does menthol inhibit metabolism of NNAL in smokers? You have one study that said no, they do not inhibit metabolism of NNAL; and one that said yes. Again, both are in human subjects; but there were some significant metrological differences.

In one study these were heavy smokers that smoked at least 15 cigarettes per day. These subjects smoked as desired, just their normal smoking behavior. They were smoking light cigarettes, which were defined by the author as seven to 15 milligrams of tar.

In the second study you had a greater variation in the number of cigarettes per day. Smokers just had to smoke at least five cigarettes per day. The smokers had overnight abstinence of both food and smoking; and that may influence enzyme activity. The cigarettes just had to be classifiable according to the FTC menthol status. So they, you know, could be light; could be not light. They just had to be classifiable as menthol versus nonmenthol. So you see that both of these

studies came up with two different outcomes.

What about toxicity and the cellular effects of menthol? In an animal study with nose-inhalation of tobacco smoke from tobacco smoke either with or without menthol. So basically smoked computer menthol cigarette or smoked from a nonmenthol cigarette.

Exposure to either cigarettes produced body weight in these rats; produced histopathological changes, such as epithelial hyperplasia and/or squamous metaplasia in the nasal passages, trachea and larynx, or lungs and bronchi. There was also olfactory epithelial degeneration.

In fact, the only difference between the rats that inhaled menthol smoke versus nonmenthol smoke was that those that inhaled nonmenthol smoke actually had a higher incident of nasal discharge.

Turning now our attention to cell membrane permeability. Tobacco smoke alters cell membranes. Whether it is menthol tobacco smoke or nonmenthol tobacco smoke. What we're looking at now is whether or not there is a difference between the menthol

versus nonmenthol tobacco smoke.

In a study by Alakayak and Knall in 2008, they found that the transepithelial electrical resistance between human bronchial epithelial cells was reduced by tobacco smoke. So usually the cells are very close together. If there is a loosening of the gap junction between the cells, that indicates cellular irritation; sort of integrity is lost between that. There was no difference between menthol versus nonmenthol smoke.

Continuing with cell membrane permeability. In a study that looked at porcine esophageal tissue, which was bathed in a solution containing both menthol and NNK -- that's one of our tobacco specific nitrosamines or carcinogens that we talked about earlier.

With the menthol there was markedly lower permeation of NNK. There was an increased tissue reservoir formation of the NNK. The result is that significantly more NNK bound within the esophageal mucosa; and it possibly increased the cell exposure to NNK.

Now, the authors of the study suggested that this may increase the likelihood of cancer of the esophagus. However, you know, there is extremely limited evidence for that statement. First, this is a single in vitro animal study. It is not an in vivo study. It is a non-human study; and as we will discuss later in the talk, the epidemiological studies are inconclusive.

What about menthol's effects on cell proliferation and cell death, cell toxicity? Menthol is toxic in vitro biologic models in normal tissue. In cancer cell cultures with a variety of cancer cell lines, menthol both dose and time-dependently inhibits cell proliferation and/or induces cell death.

However, there is -- menthol does not appear to enhance the toxicity that is already produced by tobacco smoke. So even though these things sound bad, they are just as bad as nonmenthol tobacco smoke.

Now, we turn our attention to menthol and respiration. In a published article on the publicly

available industry documents, there was an early tobacco study -- industry study that reported that mentholation of cigarettes appeared to exert an adverse affect on respiratory function.

However, most studies have failed to find any effects of menthol on respiration. This includes breathing patterns and nasal resistance. Dr. Lawrence touched upon this, this morning in her presentation.

Although inhaled menthol has been associated with reduced ratings of respiratory discomfort, there is no physiological basis for that. There is no change in nasal resistance, for example. So there is a dichotomy between the sensation of something and a physiological basis for a change in that.

What about menthol and cardiovascular function. In the CARDIA study they compared menthol to nonmenthol smokers. This is a long scale longitudinal study that we have been discussing in our previous presentation. Menthol smokers do not have significant differences in terms of coronary

calcification, or in the reduced pulmonary function. This means that tobacco smoke was harmful all the way around. The menthol did not make it more harmful when you are looking at both of the outcomes.

In a rapid smoking study, they found only a single ethnic or racial difference. Black menthol smokers had lower increases in heart rate as compared to black nonmenthol smokers. So when people smoke cigarettes there is an increase in heart rate. In this study by Caskey, in this rapid smoking study, Black menthol smokers experienced a greater increase of heart rate as compared to Black nonmenthol smokers.

So there was a four percent increase in the nonmenthol smokers compared to a 12 -- I am sorry, there was a -- yeah, four percent increase in menthol as compared to a 12 percent increase in the menthol smokers -- nonmenthol smokers; I apologize. Third one, get it right.

Continuing with cardiovascular function. In a small within-subject laboratory study which

used denicotinized cigarettes -- test cigarettes; these were either menthol or nonmenthol cigarettes that had the nicotine removed. I find it helpful to think of it as sort of how coffee can be decaffeinated. I think that might be helpful when you are visualizing it. So these are cigarettes. The nicotine has been removed.

People are smoking either menthol or nonmenthol cigarettes in a laboratory, and you are looking at cardiovascular outcomes. So menthol smokers had greater increases in heart rate in response to both kinds of cigarettes. Now, the nicotine has been taken out. Nicotine is the stimulant drug in the cigarette.

So because the menthol smokers had increases in heart rate following either the denicotinized menthol cigarettes or the denicotinized nonmenthol cigarettes, the thinking is this is some kind of smoker difference. There is not a difference between the menthol, nonmenthol test cigarettes. This is -- has something to do with the group of smokers -- the menthol smokers.

There were three cross-over laboratory studies by Ciftci and colleagues, which looked at the acute effects on two test cigarettes. So if someone smoked either two menthol cigarettes or two nonmenthol cigarettes in a cross-over study, and several cardiovascular outcomes were investigated.

There appear to be no difference on measures of coronary flow reserves comparing the two cigarettes. There appear to be worse ventricular diastolic function after smoking the menthol cigarettes. After smoking the menthol cigarettes there was also a greater increase in heart rate. You are looking at an increase of 101 beats per minute as compared to 83 beats per minute.

Following the menthol cigarettes, there was a greater increase in systolic blood pressure. There were also -- there was also greater stiffness of the carotid arteries, given as a stiffness index. So these are both menthol and nonmenthol smokers that are smoking these test cigarettes. Following the menthol cigarettes you get some significant -- significantly different outcomes in cardiovascular

outcomes, and these are considered poor outcomes.

Next, we're going to talk about menthol-induced allergic reactions and inflammation. There have been a few studies that have discussed sensitivity following menthol cigarettes. We are not discussing general allergic reactions to menthol. This is limited only to the reactions following menthol cigarettes.

And a 1951 study, a earlier study -- case study of a woman with nonthrombocytopenic purpura; itchy rash, very uncomfortable. She got this purpura following smoking menthol cigarettes. Her physician then recommended she stop smoking the menthol cigarettes. She did. The purpura was eliminated.

Then the physician said, hey, try smoking the menthol cigarettes again; let see what happens. Well, the purpura returned. However, following the cessation of using menthol cigarettes, the purpura was alleviated and didn't come back. So, it's always been an interesting case study, because there was an actual challenge in the middle of that.

In another case series it describes three young women who came -- who had symptoms of acute eosinophilic pneumonia that was associated with the initiation of smoking menthol cigarettes.

Next, we're going to turn our attention to menthol and tobacco-related disease. We're going to start with some animal studies. First of all, there is no evidence that menthol by itself causes cancer. But it may affect cancers that have been induced by other agents. We are going to go over some examples of this in the next series of slides.

First, in rats that had cancer induced in their large bowel and duodenum, menthol did not significantly alter that cancer. So if you look at the table, you will see that the number of tumors per rat, as well as the percent of rats with tumors was unchanged, whether or not the rat had been administered oral menthol or not. So menthol did not affect the incident of cancer in this induced rat model.

In another rat model, this one of mammary carcinogenesis, orally administered menthol

inhibited tumor formation and actually increased tumor latency, sort of chemopreventive. So if you look at the table what you see, as compared to control, the animals that were orally administered menthol had a fewer number of tumors per rat; and there was also a longer latency before the tumors appeared.

In a study by Gaworski and colleagues, in that study cigarette smoke condensate that was made from either menthol cigarettes or nonmenthol cigarettes that was painted on mouse skin -- the cigarette smoke condensate that was made from menthol cigarettes did not significantly alter tumor formation, latency or multiplicity of the tumors as compared to that -- the condensate made from nonmenthol cigarettes. This was a SENCAR mouse skin painting bioassays with TPA induced tumors.

Note that this -- unlike the previous animal studies where menthol was administered as a separate chemical; in this case you are looking at a tobacco smoke condensate. So the smoking of menthol cigarettes also contained the combination of

flavors, which included menthol.

Next, we are going to turn our attention to human studies. To date, there have been both case control studies, as well as surveys that have not shown that menthol alters smokers' likelihood of developing several kinds of cancers, including cancer of the lung, as well as non-lung smoking related cancers. There has also been no difference in cardiovascular disease or coronary heart disease. However, it has been suggested that there might be a menthol by gender by disease interaction.

So in two case control studies that have actually looked for a menthol by gender, by disease interaction, they failed to find any significant differences. However, in one case control study, male menthol smokers had a modestly increased risk of lung cancer. This was an odd's ratio of 1.45, and it was statistically significant.

In another case control study, the authors suggested an increased risk for male menthol smokers and lung cancer; however, this was not statistically significant. In addition, this was only in male

menthol smokers that had been smoking 32 or more pack years. So these are heavy smokers.

In a case control study looking at pharyngeal cancer, the authors suggested that male menthol smokers may have a modestly increased risk of pharyngeal cancer. This was not statistically significant.

In the last case control study, the authors again suggested that female menthol smokers had a modestly increased risk for esophageal cancer. Again, this was not statistically significant.

So discussion time. In a published analysis of publicly available tobacco industry documents, it was stated that Botanicals and additives, including menthol, can reduce, mask, or prevent smokers' awareness of adverse symptoms caused by smoking.

One hypothesis is that smokers of menthol cigarettes may not be able to perceive changes in health because of this masking. This could mean that menthol smokers may be less likely to seek treatment for ailments. It could be that even if

they do seek treatment, there is a delay in seeking treatment; and this may lead to poor medical prognoses. During the delays themselves menthol smokers will continue to smoke, which may itself exacerbate the illness due to extended exposure to carcinogens and to the smoke particulate.

In summary. The data on biomarkers, such as carbon monoxide and tobacco specific nitrosamines, are inconclusive. Menthol is a biologically active compound that may damage or kill cells; but menthol does not appear to alter the cytotoxic effects of tobacco smoke.

Menthol reduces feelings of respiratory discomfort, but there are no corresponding physiologic effects.

The data regarding the effects of menthol and the cardiovascular effects of cigarette smoke are inconclusive.

The data regarding menthol and cancer suggest a possible menthol by gender by disease interaction; very subjective. And menthol added to tobacco has been known to produce allergic reactions

in rare cases.

Yep, that's it. Clarifying questions time.

DR. SAMET: Okay. We are up to clarifying questions. Let's see, we are quickly generating a list. Jack won the sweepstakes.

DR. HENNINGFIELD: Couple of quick things. Did you see any evidence that you did not talk about of significant health benefit in humans attributable to menthol addiction to cigarettes?

DR. HOFFMAN: You mean menthol smokers versus nonmenthol smokers?

DR. HENNINGFIELD: Well, anything -- again, you looked at a lot of information.

DR. HOFFMAN: Right. Not talking about menthol as a separate chemical, just the health effects of --

DR. HENNINGFIELD: Yes, in cigarettes.

DR. HOFFMAN: To my knowledge, I did not come across any of those. There have been several -- there have been many studies that have examined outcomes in Black smokers versus White

smokers and found different outcomes, usually worse outcomes. But those studies did not look at menthol as an independent factor.

DR. HENNINGFIELD: And related to that was where there were differences in potential adverse health affects -- again, I'm looking at population. Because I think -- I think it's -- when we just say well, this study showed this; this showed that in a different population; then that's of no effect. I don't think that's the right way to look at it. If there is an affect in one population, then, that's a serious concern.

So were the effects that you were seeing -- and you know, it looked like there were not strong abrupt adverse affects. It looked like there were potential contribution of this or that. Were they population specific?

DR. HOFFMAN: They were case control studies.

DR. HENNINGFIELD: Okay. And the last one -- this is more just to -- this is much comment, but I think it's important. The focus of this

presentation was possible health effects; and I think it would just -- for everyone, I think it's important to understand that you can have direct health effects, but if menthol contributes, as you showed in at least some populations, to initiation, dependence, persistence, cessation; then, that's a mechanism by which it's contributing to cancer, heart disease, and so forth in at least certain populations. You just covered all this from initiation through. Is that your sense?

DR. HOFFMAN: Yes.

DR. HENNINGFIELD: Thank you.

DR. HOFFMAN: And I think the discussion --

DR. HENNINGFIELD: You covered a lot of ground in three talks.

DR. HOFFMAN: I think the discussion like sort of goes to your point where if there is some sort of masking of illness, you know, that could then have a direct impact on, you know, treatment outcomes, for example. Point well taken.

DR. SAMET: Greg.

DR. CONNOLLY: Boy, Allison, you did quite a bit of work. I am just sort of sitting back amazed.

We know that smoke, you know, is a complex aerosol. I think we know that nicotine -- I am sorry -- that menthol doesn't fall -- it's going to pretty much come into that aerosol. I am curious, did you look at any studies on particle size? Again, this is a characterization issue of the product and deposition; and related to that would be on inflammation.

So the question is, did you look at issues of particle size of menthol, deposition, and then potential inflammation?

DR. HOFFMAN: I would have to go back and check the bibliography to see if anything like that was in it. Off the top of my head, I don't recall seeing anything like that; but I can do back and check for you.

DR. SAMET: Actually, Greg, if I could clarify your question, maybe ask again. Are you asking the question, is menthol particle found -- in

other words in itself, not in the form of particulate matter? And we know the aerosol size distribution in general. So I don't know if this is known.

DR. HECK: I am aware, Greg, of a report from the CDC group with Battelle; and it's been presented, but not published that I'm aware of where they looked at particle size, but that was in an age -- an ETS -- well, an age, size, stream smoke chamber. It was really not relevant. It was represented as -- actually, I talked to the author, because it was a little confusion on what was presented relative to what was done. It turned out that the particle size data came from a different experiment.

DR. SAMET: Okay. I'm not sure we have got this clarified. We can tuck it away as an additional issue.

DR. CONNOLLY: I think, again, it appears to be an area that would be worth investigating.

DR. SAMET: Neal.

DR. BENOWITZ: There is an important paper

dealing with racial differences and lung cancer by Haiman in 2005 New England Journal of Medicine, which has a very interesting dose-response curve. Basically, what it shows is that the risk of lung cancer in African Americans is three times as high as Whites in people smoking relatively few cigarettes per day, like under 15. When you go up to 30 cigarettes per day, the risk is very similar.

So one of the questions, I think, regarding menthol is the risk of menthol particularly in lower cigarette consumption levels. If menthol, for example, allows or masks the harshness, or allows people to inhale more deeply, that's more likely to be important than people who are smoking three cigarettes per day and taking in more smoke per cigarettes.

A number of researchers have shown that the fewer smokes you take in per day, the more smoke you take in per cigarette. So I think the issue of the health effects of menthol need to be looked at not just in total numbers, but by cigarettes per day. I think that might be a place where an action

can occur. So if you are doing more work in this area, I think that would be very important to look at.

DR. HOFFMAN: I agree. I think it would be. I think -- but you also have -- one of the big problems that we had where you have were studies that look at racial/ethnic differences, but menthol isn't evaluated independently. So you know, it could be a mitigating factor, but the data don't actually show us that.

DR. SAMET: Dan.

DR. HECK: Yes, with regard to the epidemiology we did hear mention of numerous -- well, at least of the positive suggestion that have been seen in literature. Was there a reason that the paper of Edsall and colleagues from Margaret Spitz's group at M.D. Anderson, which was a lung cancer risk model specific for African Americans not included in that?

DR. HOFFMAN: That's actually going to be included in the White paper. Just to let people know what that study -- basically, the argument is

that because the statistical modeling for lung cancer outcomes was made using White smokers, it might not be appropriate to use that statistical model on Black smokers. In a nut shell that's what it is. You know, it's difficult to include that in this presentation, but it is included in the White paper.

DR. HECK: The paper also concluded that menthol isn't near as protective, in their words, relative to nonmenthol cigarettes. I think that's an important point for a balance consideration of all the literature. As well as there were several other comparisons in these various epi studies that are listed that also had at least point estimates of risk below 1.0; and we haven't seem those in this summary. The data, I think, would be useful for all of us to consider those in the mix.

DR. SAMET: Okay. Patricia.

DR. NEZ HENDERSON: I was wondering if there was any literature on the effects of menthol and secondhand smoke, and the impact that it has on children.

DR. HOFFMAN: That was not included in this particular bibliography.

DR. SAMET: Okay. Other clarifying questions? Yes, John.

DR. LAUTERBACH: Going to the -- I believe it is the Ciftci study back on -- at least page 11 of the slides. Is there anything we know about the composition of those menthol cigarettes versus the nonmenthol because of those differences?

DR. HOFFMAN: Which?

DR. LAUTERBACH: Slide 21.

DR. HOFFMAN: Slide 21; I was on 12.

So your question is, what were they made up of?

DR. LAUTERBACH: Yes.

DR. HOFFMAN: In the study they basically said that there were two types of cigarettes -- a menthol cigarette and a nonmenthol cigarette. I can go back and check for more detail.

DR. HECK: I can help with that answer. This was a study from Turkey. So I assume they were regional Turkey cigarettes.

DR. SAMET: Okay. Other questions?

I have just a minor one on slide eight where you mentioned the possibility that somehow other chemicals might effect carbon monoxide, I guess, uptake. Was that speculation on the part of the authors? I'm not sure I know how that would happen.

DR. HOFFMAN: That was speculation on the part of Rabinoff. Just as a potential -- you know, as a possible variable.

DR. SAMET: Okay. Okay. Thank you.

Let's see, are there other -- other questions -- clarifying questions?

The group is exhausted, at least with clarifying questions. Greg.

DR. CONNOLLY: My comment is, I want to thank you, Jon, for keeping us in time, and moving us along so swiftly.

DR. SAMET: Thanks, Greg. We will see how the rest of this goes.

So I think -- so I guess we can adjourn; or we can look at questions in relationship to our

discussion -- quick consultation.

Okay. I think I have got it. We can't talk about the questions on this paper that are called "questions to the Committee;" but should we want to formulate other questions we can; or alternatively we can wait until tomorrow.

If you look at tomorrow's agenda we will reconvene. We will have sort of a recapping of today. We have our public comment period, and then we begin the Committee discussion, which, I think, is where we really have an opportunity to have a free and -- relatively unfettered discussion of how we're going to approach our task.

So right now, I guess, we can have a somewhat fettered discussion of questions we might address. So if anybody has a clarifying question on what I just said, ask it. Greg.

DR. CONNOLLY: Jon, I just thank you for being excellent in maintaining time and moving us along. An awful lot of data was presented today. I think, you know, sometimes to think about what was presented, and to take a peek at some of the Power

Points that were presented, you know, may help in the process -- and this is my opinion; it probably also reflects a little bit of tiredness. So I'm just putting that forth.

DR. SAMET: Okay. I think that was a proposal for adjournment, if I can read between the lines.

You know, I actually think that we may be -- we may be done. This may be, perhaps, the last time that we ever end an hour and ten minutes early; but if we're going to get that added back to our lives, let's take it then.

Okay. I have to read the statement for adjournment.

Okay. Adjourn, right.

Committee members, please remember there must be no discussion of the meeting topic this evening either amongst yourselves or with the press, or with any member of the audience. Thank you.

And remember that we will reconvene in this room tomorrow morning at 8:30, and take your stuff with you. And I think that's it then; and

thanks. And I think we are off and launched.

And thanks to FDA for excellent presentations. You have done a lot of work, as everyone has pointed out; and we look forward to getting started tomorrow morning. Thank you.

(Whereupon, at 3:49 p.m., the proceedings adjourned.)

CERTIFICATE OF REPORTER

I, Stella R. Christian, A Certified Shorthand Reporter, do hereby certify that I was authorized to and did report in stenotype notes the foregoing proceedings, and that thereafter my stenotype notes were reduced to typewriting under my supervision.

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SIGNED this 14th day of April, 2010.

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STELLA R. CHRISTIAN